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(54) Title: NUCLEIC ACID MOLECULES ASSOCIATED WITH MELANOMA AND THYROID TUMORS

(57) Abstract

The present invention relates to isolated nucleic acid molecules associated with melanoma or thyroid tumors and compositions derived therefrom. The present invention further relates to methods for diagnosing and treating melanoma, thyroid tumors and other related pathological conditions such as rectal cancer, lung cancer, breast cancer and colon cancer, by employing such nucleic acid molecules and compositions.

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NUCLEIC ACID MOLECULES ASSOCIATED WITH MELANOMA AND THYROID TUMORS

FIELD OF THE INVENTION

This invention relates to isolated nucleic acid molecules associated with melanoma and thyroid tumors as well as uses thereof for diagnosing and treating melanoma and thyroid tumors.

BACKGROUND OF THE INVENTION

Recent advances in the understanding of the molecular mechanisms of antigen recognition have led to many novel immunotherapy approaches for the treatment of human cancer. One approach is by stimulating a patient's immune system with antigens that are specifically expressed by cancerous cells, i.e., tumor vaccines. Specific tumor vaccines require pre-identification of tumor associated antigens, i.e., molecules that are either specifically expressed or overexpressed in tumor cells.

Extensive efforts have been made to identify tumor associated antigens in humans by using two approaches which are referred to as the genetic approach and the biochemical approach. The genetic approach is exemplified by dePlaen et al., *Proc. Natl. Sci. USA* 85: 2275 (1988), incorporated herein by reference. In this approach, cDNA libraries prepared from antigen-positive tumor-cell lines are transfected into antigen-negative recipient cells, such as COS cells or variants of tumor cell lines. The transfectants are subsequently screened for the expression of tumor antigens which are recognized by tumor-specific cytolytic T-Lymphocyte clones ("CTLs"). The biochemical approach, exemplified by Mandelbiom et

al. *Nature* 369: 69 (1994) which is incorporated herein by reference, is based on acidic elution of peptides which are bound to MHC-class I molecules at the surface of tumor cells. Such elution produces pools of peptides which are subsequently fractionated by reverse-phase high performance liquid chromatography (HPLC). Tumor specific antigenic peptides are subsequently identified based on their ability to activate tumor-specific CTL clones.

Application of these two approaches has led to the molecular identification of new human antigens in human tumors, most notably in malignant melanoma, such as MAGE-1, Tyrosinase and MART-1. See, e.g., van der Bruggen et al., *Science* 254: 1643-1647 (1991); Brichard et al., *J. Exp. Med.* 178: 489-495 (1993); Kawakami et al., *Proc. Natl. Acad. Sci. USA* 91: 3515-3519; Cox et al., *Science* 264: 716-719 (1994).

However, these two approaches have the following disadvantages. First, such methods are enormously cumbersome, time-consuming and expensive. Second, these methods depend on the establishment of autologous tumor cells in culture and isolation of stable autologous CTL clones that recognize antigens on the cultured tumor cells. It is difficult to establish cell lines from certain types of tumors, as shown by, e.g., Oettgen, et al., *Immunol. Allerg. Clin. North. Am.* 10:607-637 (1990). In addition, malignant cell lines established from a patient which are capable of growing *in vitro* may not express the complete spectrum of tumor associated antigens of the patient's original tumor. It is also known that some epithelial cell type cancers are poorly susceptible to CTLs *in vitro*, precluding routine analysis. Third, the relevance of

an identified tumor associated antigen to the respective tumor *in vivo* remains to be proven, as the respective CTLs can be obtained not only from patients with the respective tumor, but also from healthy individuals.

These problems have stimulated the art to develop alternative methodologies. One such methodology is described by Sahin et al., *Proc. Natl. Acad. Sci. USA* 92: 11810-11913 (1995), incorporated herein by reference. Also, see U.S. Patent No. 5,698,396 and International Application WO 96/40209, both of which are incorporated herein by reference. According to this method, a cDNA library is prepared from a pathological sample of a patient, e.g., tumor cells. The library is expressed in host cells, and screened with diluted serum from a patient which has been pre-treated to remove interfering binding partners. Host cells expressing the antigens are identified by their strong reactivity toward the antibodies in the serum in a binding assay. This method is also known as the SEREX method ("Serological Identification of Antigens by Recombinant Expression Cloning").

Application of the SEREX methodology has confirmed the expression of previously identified tumor associated antigens that are associated with melanoma, renal cell carcinoma and Hodgkins' disease. Application of the SEREX methodology has also led to the identification of novel genes encoding tumor-associated antigens, such as HOM-RCC-3.11, HOM-HD-21 and NY-ESO-1. See Sahin et al. (1995); Türeci et al. (1997a), *J. Biol. Chem.* 272: 6416- 6422; Crew et al. (1995), *EMBO J.* 144: 2333-2340; Chen et al. (1997),

Proc Natl. Acad. Sci. USA 94: 1914-1918, review by Türeci et al.(1997b) *Molecular Medicine Today* 3(8): 342-349 and review by Sahin et al. (1997) *Current Opinion in Immunology* 9: 709-716 . Since the molecular identification of immunogenic proteins by the SEREX methodology is based on the reactivity of such proteins with patients' sera, immunogenic proteins which can be identified by SEREX are not restricted to cell-surface antigens and include a more complete repertoire of proteins expressed by a tumor. In fact, the SEREX methodology permits the identification of proteins which are abnormally expressed by cells of any pathological condition that are capable of eliciting a strong antibody immune response in the patient.

The antigens identified by SEREX can be classified into different categories based on the expression patterns of these antigens, as described by Türeci et al. (1997b), *Molecular Medicine Today* 3(8): 342- 349. One category of the SEREX-detected antigens are tumor-specific antigens derived from transcriptionally activated genes which are not expressed in normal tissues, such as HOM-MEL-40. Another category of the SEREX-detected antigens are differentiation antigens which are expressed in tumor cells as well as in normal cells developed from the same precursor origin, e.g., Tyrosinase. Yet another category of the SEREX-detected antigens are derived from mutated genes, such as a mutated tumor suppressor gene p53. Still another category of the SEREX-detected antigens are products of alternative splicing, e.g., the splice variant of restin (associated with Hodgkin's disease). The majority of the SEREX-detected antigens

are encoded by genes which are expressed in normal tissues and are overexpressed in tumors, e.g., HOM-HD-21 (associated with Hodgkin's disease) and carbonic anhydrase (associated with renal cancer). SEREX has also identified antigens encoded by genes which are expressed at similar levels in normal tissues and in tumors, such as CCAAT enhancer-binding protein HOM-MEL-2.4. It is proposed that this category of tumor associated antigens are detected by SEREX perhaps due to unusual protein processing, and therefore, unusual presentation of antigens in tumors. SEREX has also identified non-cancer-related autoantigens involved in, e.g., autoimmune diseases, such as NY-ESO-2' (encoding U1 snRNP).

In accordance with the present invention, the SEREX methodology has been applied to melanoma samples and thyroid tumor samples. A number of nucleic acid molecules have been isolated and sequenced. These results are the subject of this invention, which are elaborated upon the disclosure which follows.

SUMMARY OF THE INVENTION

The present invention is directed to isolation and identification of nucleic acid molecules which are associated with melanoma and thyroid tumors. In particular, ten nucleic acid molecules have been isolated by applying the SEREX methodology to melanoma samples, and ten nucleic acid molecules have been isolated by applying the SEREX methodology to thyroid tumor samples.

Accordingly, one embodiment of the present invention is directed to newly isolated nucleic acid

molecules, MEL 3, MEL7, Thy5, Thy6, Thy 11, Thy14 and Thy 15 (SEQ ID NOS: 3, 7, 14, 15, 17 and 19-20). The present invention also contemplates nucleic acid molecules, the complement sequences of which hybridize under stringent conditions to at least one of SEQ ID NOS: 3, 7, 14, 15, 17 and 19-20.

The present invention further contemplates vectors containing any one of the above nucleic acid molecules, as well as host cells transformed with such vectors. In a preferred embodiment, the present invention provides an antigen presenting cell transformed with one of such expression vectors, having an HLA/peptide complex at the cell surface.

In another embodiment, the present invention provides proteins encoded by the nucleic acid molecules of SEQ ID NOS: 3, 7, 14, 15, 17 and 19-20 or parts thereof.

Still another embodiment of the present invention provides antibodies directed towards a protein encoded by any one of the nucleic acid molecules of SEQ ID NOS: 3, 7, 14, 15, 17 and 19-20 or parts thereof.

The present invention is also directed to isolated HLA/peptide complexes, wherein the peptide is encoded by a fragment of any one of the nucleic acid molecules of SEQ ID NOS: 3, 7, 14, 15, 17 and 19-20.

A further aspect of the present invention is directed to methods for diagnosing pathological conditions characterized by an abnormal expression of at least one of the nucleic acid molecules encompassing SEQ ID NOS: 1-20. The pathological condition includes melanoma, the presence of a thyroid tumor, rectal

cancer, lung cancer, breast cancer or colon cancer. According to the present invention, the determination of the abnormal expression of a nucleic acid molecule can be made by assaying a component manifesting the expression of such molecule, such as mRNA, protein(s), antibodies in the serum, presence of specific CTLs, or cells presenting an antigenic peptide.

Another aspect of the present invention is directed to pharmaceutical compositions. The pharmaceutical compositions of the present invention can include an antisense molecule of one or more of the nucleic acid molecules encompassing any one of SEQ ID NOS: 1-20, a protein encoded by a nucleic acid molecule encompassing any one of SEQ ID NOS: 1-20 or parts of such protein, an antibody directed to such a protein, a cell presenting an antigenic peptide at the surface, a CTL generated *ex vivo* against such cell, or combinations thereof.

The subject therapeutic compositions of the present invention may be administered to a subject for treating a pathological condition in the subject, which is characterized by an abnormal expression of at least one of the nucleic acid molecules encompassing SEQ ID NOS: 1-20. Accordingly, methods of treatment are also provided by the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to isolated nucleic acid molecules that are associated with melanoma or thyroid tumors. The present invention further relates to proteins encoded by such nucleic acid molecules, antibodies directed against such proteins and cells expressing such nucleic acid

molecules. The present invention also provides pharmaceutical compositions as well as methods for diagnosing and treating melanoma, thyroid tumors and other related pathological conditions.

Nucleic acid molecules encoding tumor associated antigens have been identified by employing the SEREX methodology as described by Sahin et al.(1995). According to SEREX, samples of suspected abnormality, e.g., tumor cells, can be obtained from patients via routine clinical procedures. RNAs are purified from the freshly isolated samples for preparing a cDNA library, which is subsequently cloned into an appropriate expression vector. The choice of vectors may vary, depending on the host cells. When the host cell is a eukaryotic cell, yeast, viral or baculoviral vectors are preferred. When the host cell is a prokaryotic cell, then phage vectors are preferred, such as a λ phage vector. The resulting vector-carried library is then transformed into a host cell. The skilled artisan is familiar with the choice of host cells, including bacteria cells such as strains of *E. coli*, strains of *Pseudomonas* such as *Pseudomonas aeruginosa* or strains of *Bacillus*, yeast cells such as strains of *Saccharomyces* or *Pichia pastoris*, CHO cells such as CHO-1, COS cells such as COS-7 and insect host cells such as *Spodoptera frugiperda*. Once the host cells receive the vectors, the cells are cultivated and induced so as to express the proteins encoded by the nucleic acid molecules of the cDNA library.

The expressed proteins as well as derivatives thereof, such as posttranslationally-modified products (e.g., glycoproteins or lipoproteins) and polypeptide or peptide fragments processed therefrom, are then

contacted with a sample secured from a patient for identifying the clones of interest. A preferred sample is the patient's body fluid, such as serum. The serum may be obtained via routine clinical procedures from both autologous and non-autologous patients afflicted with the relevant pathological condition such as a tumor. Such serum is treated prior to use in order to remove components in the serum which recognize either the host cell or molecules derived from the vector other than the specific target molecule. Such pretreatment procedure is described by, e.g., Sahin et al. (1995).

When the expressed proteins and derivatives thereof are contacted with the pretreated patient's sample, the immune components present in the patient's sample, e.g., IgG, which are specific for a protein or derivative thereof will bind thereto. Preferably, the proteins and derivatives can be immobolized to a solid material, e.g., nitrocellulose, to facilitate the binding. The binding can be detected by a variety of assays, for example, assays using anti-human IgG conjugated with an identifiable label, such as an enzyme, a dye, or a radiolabel. Once positive clones are identified, i.e., clones expressing proteins or derivatives which are bound by the immune components from the patient's sample, the corresponding cDNA can be isolated and sequenced via routine procedures.

The SEREX methodology permits the identification of not only cell surface antigens, but any molecules which are abnormally expressed by cells that are capable of eliciting a strong antibody immune response in the patient. See, e.g., Türeci et al. (1997b).

By applying the SEREX methodology to human melanoma samples and thyroid tumor samples, the present invention provides the isolation and identification of nucleic acid molecules associated with melanoma (MEL 1-10) and nucleic acid molecules associated with thyroid tumors (Thy 1-3, 5-6, 9, 11-12 and 14-15), respectively (SEQ ID NOS: 1-20). These nucleic acid molecules have been compared with sequences in the databases and are resolved into both known and unknown sequences. Table II summarizes the results. Whether previously known or unknown, these isolated nucleic acid molecules have been identified by the instant invention to be associated with either melanoma or thyroid tumors.

Accordingly, one embodiment of the present invention is directed to newly isolated nucleic acid molecules that are associated with melanoma (MEL3 and MEL7) or thyroid tumors (Thy 5-6, 11 and 14-15). In particular, the present invention contemplates isolated nucleic acid molecules having a sequence as set forth in any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20.

The term "associated" or "association" is used herein to indicate that a relevant nucleic acid molecule is abnormally expressed in melanoma or thyroid tumors. These nucleic acid molecules may also be expressed by cells other than melanoma cells or thyroid tumor cells, e.g., cells of other types of tumors, or cells of other disorders such as an autoimmune disorder. For example, the present invention has also shown that the isolated nucleic acid molecules scored positive in the SEREX screening assay using sera from patients having rectal, lung, breast or colon cancer, indicating that an abnormal expression of these nucleic

acid molecules is also present in rectal, lung, breast or colon cancer.

The term "abnormal expression" as used herein refers to an expression that is not present in normal cells or an expression that is present in normal cells at a lower level. In the present invention, "an abnormal expression" can also be used to refer to an unusual processing of the protein expressed from a nucleic acid, which is not present in normal cells and which results in unusual presentation of antigenic peptides at the cell surface.

Another embodiment of the present invention is directed to nucleic acid molecules, the complement sequences of which hybridize under stringent conditions to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20.

"Stringent conditions" as used herein refer to conditions such as those specified in US Patent No. 5,342,774, i.e., 18 hours of hybridization at 65°C, followed by four one-hour washes with 2x SSC, 0.1% SDS, and a final wash with 0.2x SSC, more preferably 0.1x SSC, and 0.1% SDS for 30 minutes, as well as alternate conditions which afford the same level of stringency, and more stringent conditions.

In accordance with the present invention, molecules having a sequence, the complementary sequence of which hybridizes under stringent conditions to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20, can include nucleic acid molecules having substantial homology to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20; parts of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20; degenerate sequences; and modified forms of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20, such as mutant forms with base pair substitutions, deletions or insertions. In

the event that SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 are fragments of full-length genes, such genes are also contemplated by the present invention as nucleic acid molecules having a sequence, the complementary sequence of which hybridizes under stringent conditions to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20.

As used herein, "a part" of a nucleic acid molecule refers to a fragment of the nucleic acid molecule having sufficient length to encode an antigenic peptide of at least 8 or 9 amino acids. In particular, the present invention contemplates "unique" fragments of nucleic acid molecules of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20. A unique fragment is one that is a "signature" for the larger nucleic acid molecule. It is, for example, long enough to selectively distinguish the sequence of interest from others. As will be recognized by those skilled in the art, the size of the unique fragment will depend upon its conservancy in the genetic code. Thus, some regions of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 will require longer segments to be unique while others will require only shorter segments, typically between 12 and 32 nucleotides. Those skilled in the art are well versed in methods for selecting such sequences, e.g., by comparing the sequence of the fragment to those in known databases. *In vitro* confirmatory hybridization and sequencing analysis may also be used. According to the present invention, the unique fragments do not include sequences present in the prior art, such as ESTs and the like. Further according to the present invention, a unique fragment can be a functional fragment. A functional fragment of a nucleic acid molecule of the present invention is a fragment which

retains some functional property of the larger nucleic acid molecule, such as a fragment that encodes an antigenic epitope associated with melanoma or thyroid tumors.

The skilled artisan is fully capable of making, by following routine procedures, a nucleic acid molecule, the complement sequence of which hybridizes under stringent conditions to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20. The skilled artisan can determine, for example, whether SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 encompasses a complete open reading frame, and if not, can isolate the full length molecules that encompass a complete open reading frame by following standard procedures, e.g., DNA hybridization-based cloning. See, e.g., Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, New York.

The skilled artisan is also able to make fragments of these isolated nucleic acid molecules by using standard recombinant cloning techniques. The skilled artisan can further determine whether a fragment of an isolated nucleic acid molecule encodes the antigen(s) responsible for the immune response elicited in the patient and the resulting hyper-immunoreactive serum. This can be accomplished by following a number of well-known methods. For example, various portions of a nucleic acid molecule can be cloned into an appropriate expression vector which can be subsequently introduced into a desired host cell. Afterwards, polypeptides or peptides expressed from the respective DNA fragments can be tested for antigenicity by, e.g., using the patient's serum in a binding assay

routinely used in the SEREX methodology as described hereinabove; or using CTL clones with pre-defined specificity. Alternatively, one skilled in the art can chemically synthesize polypeptide or peptide fragments directly based on the nucleotide sequence of a fragment, and the antigenicity of the peptide can be determined by the reactivity toward the patient's serum in a binding assay, for example.

The skilled artisan is also able to isolate nucleic acid molecules having substantial homology to any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 by following standard procedures, e.g., DNA hybridization-based cloning procedure. See, e.g., Sambrook et al. (1989).

In another embodiment, the nucleic acid molecules of the present invention or parts thereof have been inserted into expression vectors. The choice of vectors can be determined by those skilled in the art. When the host cell is a eukaryotic cell, viral (e.g., retroviral, adenoviral or pox), yeast or baculoviral vectors are preferred. When the host cell is a prokaryotic, then phage vectors are preferred, such as a λ phage vector. It is routine for those skilled in the art to construct expression vectors in which a nucleic acid molecule of interest is placed in operable linkage to a desired promoter so as to effect the expression of the polypeptide or peptide encoded by such nucleic acid molecule in host cells. See, e.g., Sambrook et al. (1989).

The present invention also provides expression vectors which include nucleic acid molecules encoding a series of epitopes, known as "polytopes" (Thompson et al. (1995) in *Proc. Natl. Acad. Sci. USA*

92: 5845-5849; Gilbert et al., *Nature Biotechnol.* 15: 1280- 1284, 1997). The epitopes can be arranged in sequential or overlapping fashion, with or without the natural flanking sequences, and can be separated by unrelated linker sequences if desired. The polytope is processed in host cells to generate individual epitopes which can be recognized by the immune system. Thus, for example, peptides derived from the polypeptide having an amino acid sequence encoded by any one of the nucleic acid molecules of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 of the instant invention, which are presented by MHC molecules and recognized by CTL or T helper lymphocytes can be combined with peptides from other tumor rejection antigens (e.g., by preparation of hybrid nucleic acids or polypeptides) to form "polytopes". Exemplary tumor associated peptide antigens that can be administered to induce or enhance an immune response are derived from tumor associated genes and encoded proteins including MAGE-1, MAGE-2, MAGE-3, MAGE-4, MAGE-5, MAGE-6, MAGE-7, MAGE-8, MAGE-9, MAGE-10, MAGE-11, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, BAGE-1, RAGE-1, LB33/MUM-1, DAGE, NAG, MAGE-Xp2, MAGE-Xp3, MAGE-Xp4, tyrosinase, brain glycogen phosphorylase, Melan-A, and MAGE-C1. For example, antigenic peptides characteristic of tumors include those listed in Table I below.

Table I: Exemplary Antigens

Gene	MHC	Peptide	Position	SEQ ID NO:
MAGE-1	HLA-A1	EADPTGHSY	161-169	21
	HLA-Cw16	SAYGEPRKL	230-238	22
MAGE-3	HLA-A1	EVDPIGHLY	168-176	23
	HLA-A2	FLWGPRALV	271-279	24
	HLA-B44	MEVDPIGHLY	167-176	25
BAGE	HLA-Cw16	AARAVFLAL	2-10	26
GAGE-1,2	HLA-Cw16	YRPRPRRY	9-16	27
RAGE	HLA-B7	SPSSNRIRNT	11-20	28
GnT-V	HLA-A2	VLPDVFIRC(V)	2-10/11	29
MUM-1	HLA-B44	EEKLIVVLF	exon 2/ intron	30
		EEKLSVVLF (wild type)		31
CDK4	HLA-A2	ACDPHSGHFV	23-32	32
		ARDPHSGHFV (wild type)		33
β-catenin	HLA-A24	SYLDSGIHF	29-37	34
		SYLDSGIHS (wild type)		35
Tyrosinase	HLA-A2	MLLAVLYCL	1-9	36
	HLA-A2	YMNGTMSQV	369-377	37
	HLA-A2	YMDGTMSQV	369-377	38
	HLA-A24	AFLPWHRLF	206-214	39
	HLA-B44	SEIWRDIDF	192-200	40
	HLA-B44	YEIWRDIDF	192-200	41
	HLA-DR4	QNILLSNAPLGPQFP	56-70	42
	HLA-DR4	DYSYLQDSDPDSFQD	448-462	43
Melan-A^{MART-1}	HLA-A2	(E)AAGIGILTV	26/27-35	44
	HLA-A2	ILTVILGVL	32-40	45
gp100^{Pmel117}	HLA-A2	KTWGQYWQV	154-162	46
	HLA-A2	ITDQVPFSV	209-217	47
	HLA-A2	YLEPGPVTA	280-288	48
	HLA-A2	LLDGTATLRL	457-466	49
	HLA-A2	VLYRYGSFSV	476-485	50
DAGE	HLA-A24	LYVDSLFFL	301-309	51
MAGE-6	HLA-Cw16	KISGGPRISYPL	292-303	52

The peptides of SEQ ID NOS: 41, 51 and 52 are presented in U.S. Application Serial No. 08/724,774, PCT Application Publication No. WO96/10577 and U.S. Application Serial No. 08/713,354, respectively. Other exemplary peptides include those listed in U.S. Patent

Applications 08/672,351, 08/669,590, 08/487,135, 08/530,569 and 08/880,693. Other examples are known to one of ordinary skill in the art (for example, see Coulie, *Stem Cells 13*: 393-403, 1995), and can be used in the invention in a like manner as those disclosed herein.

It is known that tumors express a set of tumor antigens, of which only certain subsets may be expressed in the tumor of any given patient. Polytopes can be prepared which correspond to the different combination of epitopes representing the subset of tumor rejection antigens expressed in a particular patient. Polytopes also can be prepared to reflect a broader spectrum of tumor rejection antigens known to be expressed by a tumor type.

The present invention further contemplates host cells for propagating and/or expressing the nucleic acid molecules of the present invention. Those skilled in the art are equally familiar with the choice of cell lines and the procedures to transform or transfect such cell lines. Examples of the cell lines include, but are not limited to, eukaryotic cells such as COS cells (e.g., COS-7), CHO cells (e.g., CHO-1), NIH 3T3 cells, yeast cells (e.g., strains of *Saccharomyces* or *Pichia pastoris*), insect cells (e.g., *Spodoptera frugiperda)*; and prokaryotic cells such as strains of *E. coli*, strains of *Pseudomonas* (e.g., *Pseudomonas aeruginosa*) or strains of *Bacillus*.

In a preferred embodiment, the present invention provides an antigen presenting cell transformed with an expression vector as described hereinabove.

"Antigen presenting cells" as used herein refer to cells expressing at least one MHC class I or class II molecule, which include, but are not limited to, professional antigen presenting cells such as B cells, monocytes, macrophages, dendritic cells and T cells; and falcutative antigen presenting cells such as fibroblasts and endothelium cells. Antigen presenting cells can be isolated from tissue or blood samples. Both normal and malignant cells can be employed. Cell lines established in tissue culture from such samples can also be used. Many such cell lines are available from American Type Culture Collection (ATCC), Rockville, Maryland. Those skilled in the art can determine whether a chosen antigen presenting cell expresses at least one MHC molecule that is capable of presenting a peptide derived from a particular nucleic acid molecule. See, e.g., Coligan et al. (1994). Such cell can then be transfected with an expression vector which, under appropriate conditions, leads to the expression on the cell surface of one or more antigenic peptides encoded by fragments of the nucleic acid molecule of interest, complexed with appropriate MHC molecules,.

Another embodiment of the present invention is directed to proteins encoded by the isolated nucleic acid molecules of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 or parts thereof.

The term "protein" used herein refers to both the unmodified forms (precursors) and post-translationally modified forms of a protein. Eukaryotic cells are well known for their ability to post-translationally modify proteins, so as to produce glycoproteins and lipoproteins, for example. According

to the present invention, the term "protein" also encompasses polypeptides and peptides.

The term "polypeptide" as used herein refers to a chain of at least 10 contiguous amino acids. The term "peptide" used herein refers to a chain of at least 8 or 9 amino acids.

The protein encoded by a nucleic acid molecule can be produced by routine recombinant expression in a desired host cell and subsequently purified by various known procedures, such as chromatography. A polypeptide or peptide can also be chemically synthesized according to its coding sequence in a standard peptide synthesizer. Those skilled in the art can also isolate antigenic peptides directly from the MHC/peptide complexes of antigen-expressing cells by, e.g., a method disclosed by Mandelbiom et al.(1994). According to such method, peptides are eluted from the MHC-peptide complexes at the surface of antigen-expressing cells. The resulting pools of peptides are fractionated by HPLC and screened with antigen-specific CTL clones. Specific antigenic peptides can be identified and isolated based upon their ability to provoke specific CTL clones.

Purified proteins can be used as immunogens, either alone or in combination with an adjuvant such as saponins, GM-CSF, or interleukins. Immunogens such as these may be used, for example, to generate antibodies.

Accordingly, the present invention also contemplates antibodies directed against the proteins encoded by the nucleic acid molecules of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20 or parts thereof.

There are a variety of ways to obtain specific antibodies. Antibodies can be generated by

administering a protein of interest, either alone or in combination with an adjuvant, to various hosts, such as a rabbit, a mouse, or a sheep. Both monoclonal or polyclonal antibodies can be obtained using such immunized host. The methods for generating polyclonal and monoclonal antibodies are well known in the art. See, e.g., Coligan et al. *Current Protocols in Immunology*, John Wiley & Sons Inc., New York, New York (1994). Fragments of antibodies, such as Fab, $F(ab)_2$' and the like, as well as recombinantly produced antibodies, are also contemplated by the present invention.

Another embodiment of the present invention is directed to isolated peptide/HLA complexes. Preferably, the peptide in such isolated peptide/HLA complexes is encoded by a fragment of any one of SEQ ID NOS: 3, 7, 14-15, 17 and 19-20.

According to this embodiment, once the type of the HLA molecule capable of presenting a peptide is ascertained, such HLA molecule can be produced by any appropriate recombinant expression system, e.g., an *E. coli*-based expression system. As described above, peptides can be obtained by a number of ways, such as chemical synthesis or recombinant expression. The peptides and the presenting HLA molecules can then be mixed *in vitro* under conditions that favor the formation of HLA/peptide complexes. Such conditions are well known in the art. See, e.g., Garboczi et al. (*Proc. Natl. Acad. Sci. USA* 89: 3429-3433, 1992 and Altman et al. (*Science* 274: 94-96, 1996).

In another embodiment, the present invention provides methods of diagnosing a pathological condition

characterized by an abnormal expression of one or more of the nucleic acid molecules of the present invention.

The term "diagnosing" as used herein encompasses determining or monitoring the onset of, the progression of, the regression of, or the efficacy of a therapeutic regime for, a pathological condition.

Pathological conditions characterized by an abnormal expression of one or more of the nucleic acid molecules SEQ ID NOS: 1-30 of the present invention include, but are not limited to melanoma, the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer and colon cancer.

Diagnosis of a pathological condition can be accomplished by determining an abnormal expression of at least one, i.e., one or more, nucleic acid molecule that is associated with such pathological condition. By comparing the expression in a sample from a patient suffering a pathological condition, with the expression in a normal sample, the skilled artisan can readily determine whether a relevant nucleic acid molecule is abnormally expressed in such pathological condition.

The abnormal expression of a nucleic acid molecule can manifest as an abnormal level of the mRNA of such nucleic acid molecule, the protein or peptide fragments encoded by such nucleic acid molecule, serum antibodies against such protein or peptide fragments, peptide/MHC complexes at the cell surface, or CTLs specific for certain peptide/MHC complexes. Accordingly, there are various assays which can be employed to detect the abnormal expression of a subject nucleic acid molecule.

A sample of suspected abnormality can be taken from a patient, such as a tissue biopsy sample,

or body fluid sample such as serum. The expression of a protein of interest in such sample can be determined by a variety of diagnostic assays.

One type of diagnostic assay is based on determination of the level of mRNA of a nucleic acid molecule associated with the pathological condition in question. Thus, for example, diagnosis of melanoma can be based on assaying the level of mRNA of, preferably, the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67-encoding gene (SEQ ID NOS: 23 and 24), the CENP-B-encoding gene (SEQ ID NO: 25), or nucleic acid sequences encompassing SEQ ID NO: 3 or 7. Diagnosis of thyroid tumors can be based on assaying the level of mRNA of, preferably, the TAFII68-encoding gene (SEQ ID NO: 26), lipocortin II-encoding gene (SEQ ID NO: 27), the thyroglobulin-encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceradimase-encoding gene (SEQ ID NO: 30), or nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20. Similarly, diagnosis of rectal, lung, breast, colon cancer or any other pathological condition can be based on assaying the level of the mRNA of one or more of SEQ ID NOS: 3, 7, 14-15, 17, 19-30 that are associated with the relevant pathological condition. For example, diagnosis of rectal cancer can be based on_determining the level of preferably, the mRNA of one or more of SEQ ID NOS: 21-24, 26, or 30, or the mRNA of a nucleic acid molecule encompassing any one of SEQ ID NOS: 14-15 or 20. Diagnosis of lung cancer can be based on determining the level of preferably, the mRNA of one or more of SEQ ID NOS: 21 and 23-25, or the mRNA of a nucleic acid molecule encompassing any one of SEQ ID

NOS: 14-15 or 20. Diagnosis of breast cancer can be based on determining the level of, preferably, the mRNA of any one of SEQ ID NOS: 23 or 24, or the mRNA of a nucleic acid molecule encompassing SEQ ID NOS: 15. Diagnosis of colon cancer can be based on determining the level of preferably, the mRNA of one or more of SEQ ID NOS: 21-24, 26 or 29-30, or the mRNA of a nucleic acid molecule encompassing any one of SEQ ID NOS: 14-15 or 19-20. The methods for determining the level of mRNA are well within the ken of those skilled in the art, such as Northern Blot analysis or PCR analysis.

Another type of diagnostic assay is based on determination of the amount of protein expressed from the nucleic acid molecules associated with the pathological condition in question, or parts of such proteins. For example, for diagnosing melanoma, the protein to be examined can be the repressor protein encoded by SEQ ID NO: 21, the protein encoded by KIAA0201 (SEQ ID NO: 22), Ki-67 antigen (encoded by SEQ ID NO: 23 or 24), CENP-B (encoded by SEQ ID NO: 25) or the protein encoded by any one of the nucleic acid sequences encompassing SEQ ID NO: 3, or 7. Preferably, diagnosis of melanoma is based on detecting proteins encoded by any one of SEQ ID NOS: 1-10. For diagnosing thyroid tumors, the protein to be examined can be TAFII68 (encoded by SEQ ID NO: 26), lipocortin II (encoded by SEQ ID NO: 27), thyroglobulin (encoded by SEQ ID NO: 28), thymosin (encoded by SEQ ID NO: 29), the acid ceradimase (encoded by SEQ ID NO: 30), or a protein encoded by any one of the nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20. Preferably, diagnosis of the presence of a thyroid tumor is based on detecting proteins encoded by

any one of SEQ ID NOS: 11-20. Similarly, diagnosis of rectal, lung, breast or colon cancer, or any other pathological condition can be based on assaying one or more proteins encoded by any one, i.e., one or more, of SEQ ID NOS: 1-30, that is associated with the relevant cancer. One skilled in the art can use various assays including, e.g., SDS-gels or 2D gels, Western Blot Analysis, ELISA and immunofluorescence flow-cytometry.

Still another type of diagnostic assay is based on detection of antibodies in the serum that are specific for a protein associated with a pathological condition in question or parts of such protein. Thus, in this type of assay, antibodies are detected by using the specific antigens in assays such as Western Blot or affinity chromatography, or a SEREX screening assay described herein. Antibodies specific for an antigenic peptide can also be detected by using cells which express and present the antigenic peptide at the surface in the context of an MHC molecule via assays such as FACS.

Another type of diagnostic assay is based on detection of cells in the patient's sample, which cells have at their surface, a peptide encoded by a fragment of a nucleic acid molecule associated with the pathological condition in question. For example, for diagnosing melanoma, such nucleic acid molecule includes the gene encoding the repressor protein (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B-encoding gene (SEQ ID NO: 25), or the nucleic acid sequences encompassing SEQ ID NO: 3, or 7; and preferably, such nucleic acid molecule is any one of SEQ ID NOS: 1-10. For diagnosing thyroid tumors, such

nucleic acid molecule includes genes encoding TAFII68 (SEQ ID NO: 26), lipocortin II (SEQ ID NO: 27), thyroglobulin (SEQ ID NO: 28), thymosin (SEQ ID NO: 29), or the acid ceramidase-encoding gene (SEQ ID NO: 30), or any one of the nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20; and preferably, such nucleic acid molecule is any one of SEQ ID NOS: 11-20. Likewise, for diagnosing rectal, lung, breast or colon cancer, the nucleic acid molecule can include any one of SEQ ID Nos: 1-30 that is associated with the relevant cancer. To determine the presence of such cell in a patient's sample, cellular-immuno assays can be employed, e.g., FACS analysis using antibodies raised against such peptide, or cytotoxic assays using pre-established CTLs specific for such peptide.

Another type of diagnostic assay is based on detection of CTLs in the patient's sample that are specific for a peptide of a protein associated with the pathological condition in question. Methods for detecting CTLs specific for an antigen are known in the art and are described hereinabove, such as assays for ^{51}Cr release, TNF production or IFN-gamma production.

According to the present invention, the present methods of diagnosis are applicable not only to the pathological conditions exemplified, such as melanoma, the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer or colon cancer, but also to pathological conditions in general that are characterized by an abnormal expression of one or more of the subject nucleic acid molecules of the present invention. The isolated nucleic acid molecules of the present invention are clearly expressed in an abnormal

manner in patients having melanoma, thyroid tumor, rectal, lung, breast or colon cancer. These molecules may also be expressed abnormally in other tumors or in cells associated with other pathological disorders. Thus, the techniques described hereinabove can be employed for diagnosing a pathological condition characterized by an abnormal expression of one of the nucleic acid molecules having a sequence encompassing one or more of SEQ ID NOS: 1-20.

In another embodiment, the present invention provides pharmaceutical compositions. The pharmaceutical compositions of the present invention are useful for treating pathological conditions characterized by an abnormal expression of one or more of the instant nucleic acid molecules of the present invention.

One pharmaceutical composition of the present invention includes an antisense molecule of one of the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B encoding gene (SEQ ID NO: 25), nucleic acid sequences encompassing SEQ ID NO: 3, or 7, the TAFII68-encoding gene (SEQ ID NO: 26), lipocortin II-encoding gene (SEQ ID NO: 27), the thyroglobulin -encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceramidase-encoding gene (SEQ ID NO: 30), and nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts of such nucleic acid molecules. Preferably the antisense molecule is about 10-100 nucleotides in length and is carried by a suitable vector, such as a retroviral vector or a viral vector. The choice of vectors for such purpose is well-known in

the art, e.g., Vaccinia. The use of antisense molecules for inhibiting gene expression is known in the art.

Another pharmaceutical composition of the present invention includes a protein encoded by one of the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B encoding gene (SEQ ID NO: 25), nucleic acid sequences encompassing SEQ ID NO: 3, or 7, the TAFII68-encoding gene (SEQ ID NO: 26), lipocortin II-encoding gene (SEQ ID NO: 27), the thyroglobulin-encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceramidase-encoding gene (SEQ ID NO: 30), nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts of such nucleic acid molecules. Preferably, the protein is encoded by one of SEQ ID NOs: 1-20 or parts thereof. Such proteins can be administered to a subject to provoke or augment an immune response in the subject against the abnormally expressed proteins.

Still another pharmaceutical composition of the present invention includes an antibody specific for a protein encoded by one of the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B encoding gene (SEQ ID NO: 25) and nucleic acid sequences encompassing SEQ ID NO: 3, or 7, the TAF 1168-encoding gene (SEQ ID NO: 26), lipocortin II-encoding gene (SEQ ID NO: 27), the thyroglobulin-encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceramidase-encoding gene (SEQ ID NO: 30), and nucleic acid sequences

encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts of these nucleic acid molecules. Preferably, the antibody is specific for a protein encoded by any one of SEQ ID NOs: 1-20 or parts of such proteins. Both polyclonal antibodies and monoclonal antibodies can be used. Monoclonal antibodies are preferred.

Another pharmaceutical composition of the present invention includes an antigen-presenting cell having at the cell surface, in the context of MHC molecules, one or more antigenic peptides encoded by a fragment(s) of one of the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B encoding gene (SEQ ID NO: 25) and nucleic acid sequences encompassing SEQ ID NO: 3, or 7, the TAFII68-encoding gene (SEQ ID NO: 26), lipocortin II -encoding gene (SEQ ID NO: 27), the thyroglobulin-encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceramidase-encoding gene (SEQ ID NO: 30), nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20. The antigen presenting cells to be used in the pharmaceutical composition of the present invention express MHC molecules that are compatible with the MHC molecules of the patient being treated. At least one of the MHC molecules expressed by such cells is capable of presenting a peptide encoded by a fragment of a subject nucleic acid molecule. The choice of antigen presenting cells is described hereinabove.

In accordance with the present invention, antigen presenting cells can be further modified to express other molecules for augmenting immunogenicity. A number of immune response potentiating molecules can

be used, including lymphokines, costimulatory molecules such as B7-1 (CD80), B7-2(CD86), LFA-3, LFA-1 and CD40. B7 molecules, by interacting with CD28 or CTLA-4 molecules on T cells, potentiate T cell proliferation and effector function such as antitumor activity. See, e.g., Zheng et al., *Proc. Natl. Acad. Sci. USA* 95: 6284-6289 (1998); Wang et al., *J. Immunol.* 19: 1-8 (1996). The interaction of LFA-3 on antigen presenting cells with CD2 on T cells induces T cell to produce IL-2 and IFN-gamma (Fenton et al., *J. Immunol.* 21(2): 95-108, 1998). Complete CTL activation and effector function requires Th cell help through the interaction between the CD40 ligand expressed on Th cells and the CD40 molecules expressed on antigen presenting cells (Ridge et al., *Nature* 393:474, 1998; Bennett et al., *Nature* 393: 478, 1998; and Achoenberger et al., *Nature* 393: 480, 1998). These additional immune-potentiating molecules can be included in any of the expression vectors (such as retroviral, adenoviral, or pox vectors) and introduced into antigen presenting cells by, e.g., transfection.

The pharmaceutical compositions of the present invention can also include a pharmaceutical acceptable carrier. As used herein, a pharmaceutically acceptable carrier includes any and all solvents, including water, dispersion media, culture from cell media, isotonic agents and the like that are non-toxic to the patient. Preferably, it is an aqueous isotonic buffered solution with a pH of around 7.0. The use of such media and agents in therapeutic compositions is well known in the art. Except insofar as any conventional media or agent is incompatible with the pharmaceutical compositions of the present invention,

use of such conventional media or agents in the pharmaceutical compositions are contemplated. Supplementary active ingredients can also be incorporated into the compositions.

In a further embodiment, the pharmaceutical compositions of the present invention are used to treat pathological conditions characterized by an abnormal expression of one or more of the instant nucleic acid molecules of the present invention. Accordingly, the present invention provides methods of treating a subject suffering a pathological condition characterized by an abnormal expression of one or more of the instant nucleic acid molecules, by administering to such subject a therapeutically effective amount of a pharmaceutical composition of the present invention.

The term "treating" means delaying the onset of a pathological condition or alleviating a pathological condition by controlling the expression of the nucleic acid molecule being abnormally expressed under such pathological condition. "Alleviating" is indicated by, in the case of tumor, inhibition of tumor growth, reduction in tumor size, inhibition of tumor metastasis and the like.

"A pathological condition" as defined hereinabove, includes, but is not limited to, melanoma the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer or colon cancer. For treating melanoma, pharmaceutical compositions derived from melanoma-associated nucleic acid molecules (such as antisense molecules, proteins, antibodies or cells) are preferred. For treating thyroid tumors, pharmaceutical compositions derived from thyroid tumor-associated nucleic acid molecules are preferred. Likewise, for

treating any other pathological condition, such as rectal cancer, lung cancer, breast cancer or colon cancer, preferred pharmaceutical compositions to be used in the treatment are those derived from the nucleic acid molecules associated with that condition.

One method of treating a subject having a pathological condition characterized by an abnormal expression of a nucleic acid molecule of the present invention is by administering to the subject, an antisense molecule of such nucleic acid molecule or parts thereof. For example, a subject having melanoma can be treated by administering to the subject, one or more of an antisense molecule of the repressor protein-encoding gene (SEQ ID NO: 21), the KIAA0201 gene (SEQ ID NO: 22), the Ki-67 encoding gene (SEQ ID NO: 23 and 24), the CENP-B encoding gene (SEQ ID NO: 25), or nucleic acid sequences encompassing SEQ ID NO: 3, or 7, or parts of these nucleic acid molecules; a subject having thyroid tumors can be treated by administering to the subject one or more of an antisense molecule of the TAFII68-encoding gene (SEQ ID NO: 26), lipocortin II-encoding gene (SEQ ID NO: 27), the thyroglobulin-encoding gene (SEQ ID NO: 28), the thymosin-encoding gene (SEQ ID NO: 29), the acid ceramidase-encoding gene (SEQ ID NO: 30), and nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts of these nucleic acid molecules.

Preferably, the antisense molecule is contained in a vector suitable for expression in the subject being treated. The choice of vectors for such purpose is well-known in the art and can be viral or retroviral vectors, e.g., a Vaccinia vector. A vector carrying the antisense DNA can be administered to a

subject in an amount sufficient to inhibit the expression of the protein. Such vector can be administered alone or with a carrier, such as a liposome, which facilitates the incorporation of the vector into a cell.

Another method of treating a subject having a pathological condition characterized by an abnormal expression of a nucleic acid molecule of the present invention is by administering to the subject, a protein encoded by such nucleic acid molecule or parts thereof. For example, a subject having melanoma can be treated by administering to the subject, the repressor protein (encoded by SEQ ID NO: 21), the protein encoded by KIAA0201 (SEQ ID NO: 22), Ki-67 (encoded by SEQ ID NO: 23 or 24), CENP-B (encoded by SEQ ID NO: 25), a protein encoded by any one of the nucleic acid sequences encompassing SEQ ID NO: 3, or 7, or parts or combinations thereof. A subject having thyroid tumors can be treated by administering to the subject, TAF II68 (encoded by SEQ ID NO: 26), lipocortin II (encoded by SEQ ID NO: 27), thyroglobulin (encoded by SEQ ID NO: 28), thymosin (encoded by SEQ ID NO: 29), the acid ceradimase encoded by SEQ ID NO: 30), a protein encoded by any one of the nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts or combinations thereof.

The proteins are administered in an amount sufficient to provoke or augment an immune response in the subject which eliminate the abnormally expressed proteins. The proteins can be combined with one or more of the known immune adjuvants, such as saponins, GM-CSF, interleukins and so forth. Small peptides may

also be coupled to the well-known conjugates to achieve the desired immunogenicity.

Still another method of treating a subject having a pathological condition characterized by an abnormal expression of a nucleic acid molecule of the present invention is by administering to the subject, an antibody directed against the protein encoded by such nucleic acid molecule or parts thereof. For example, a subject having melanoma can be treated by administering to the subject, one or more of an antibody directed against the repressor protein (encoded by SEQ ID NO: 21), the protein encoded by the KIAA0201 (SEQ ID NO: 22), Ki-67 (encoded by SEQ ID NO: 23 or 24), CENP-B (encoded by SEQ ID NO: 25), or a protein encoded by any one of the nucleic acid sequences encompassing SEQ ID NO: 3, or 7, or parts of these proteins. A subject having thyroid tumors can be treated by administering to the subject, one or more of an antibody directed against TAFII68 (encoded by SEQ ID NO: 26), lipocortin II (encoded by SEQ ID NO: 27), thyroglobulin (encoded by SEQ ID NO: 28), thymosin (encoded by SEQ ID NO: 29), the acid ceradimase (encoded by SEQ ID NO: 30), or a protein encoded by any one of the nucleic acid sequences encompassing one of SEQ ID NOS: 14-15, 17 and 19-20, or parts of these proteins. The antibodies can be administered alone or with pharmaceutically acceptable carriers in an amount sufficient to inhibit the function of the protein or proteins.

Still another method of treating a subject having a pathological condition characterized by an abnormal expression of a nucleic acid molecule of the present invention is by administering to the subject,

an antigen presenting cell having one or more antigenic peptides complexed with MHC molecules, which peptides are encoded by fragments of such nucleic acid molecule.

The cells are preferably treated to be rendered non-proliferative before the administration to the subject suffering a relevant pathological condition. The cells are administered to a patient in an amount sufficient to stimulate an immune response against the protein that is abnormally expressed in the patient. Such cells may present epitopes to T cells and/or B cells, leading to a cellular immune response and/or a humoral immune response in the subject. According to the present invention, the induced immune response can alleviate the pathological condition by cytotoxic killing and/or antibody-mediated killing of the cells of abnormality.

In addition to direct administration to a subject for treatment, antigen presenting cells expressing an MHC/peptide complex of interest can be used in an *ex vivo* regime to generate cytolytic T cells specific for the peptide being presented. The procedure to develop such specific CTLs *in vitro* is known in the art, e.g., as disclosed by the United States Patent No. 5,342,774. Briefly, a blood sample containing T cell precursors is taken from a subject, preferably, the autologous patient. PBLs are purified from such blood sample and are incubated with stimulator cells, in this case, the antigen presenting cells expressing a MHC/peptide complex. Specific CTLs are thus produced which can be detected by standard assays, such as Cr^{51} release or secretion of IFN-gamma. CTL cells generated as such can be reperfused to the patient and alleviate the pathological condition by

lysing the cells abnormally expressing the peptide/MHC complex. See related teachings by Greenberg (1986) *J. Immunol. 136 (5)*: 1917; Riddel et al. (1992) *Science 257*: 238; Lynch et al. (1991) *Eur. J. Immunol. 21*: 1403; and Kast et al. (1989) *Cell 59*: 603.

For practicing the treatment methods of the present invention, a pharmaceutical composition as described hereinabove can be administered to a patient in need thereof in any convenient manner, e.g., by subcutaneous (s.c.), intraperitoneal (i.p.), intra-arterial (i.a.), or intravenous (i.v.) injection..

The precise amount of a pharmaceutical composition to be administered so as to be therapeutically effective, can be determined those skilled in the art with consideration of individual differences in age, weight, tumor size, severity of the pathological condition and so forth.

All the publications mentioned in the present disclosure are incorporated herein by reference. The terms and expressions which have been employed in the present disclosure are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.

The present invention is further illustrated but not limited by the following examples.

Example 1

Isolation of cDNA clones using the SEREX methodology.

Two thyroid tumor cDNA libraries and one melanoma cDNA library were prepared, using standard techniques. See Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, New York. The libraries were screened using the SEREX methodology as described supra and set forth by Sahin et al. (1995) and by Chen et al., *Proc. Natl. Acad. Sci. USA 94*: 1914 (1997), incorporated herein by reference.

More specifically, total RNA was isolated from tumor cells secured from three individuals, Patient 1 with melanoma, Patients 2 and 3 with thyroid tumors. The RNA from each patient was used to prepare a cDNA library, resulting in three cDNA libraries, named as Mel-N1, Thy-N1, and Thy-N2, respectively. Each of these cDNA libraries was cloned into λZAP phage vectors (Short et al., *Nucleic Acids Res. 16*: 7583, 1988). Bacteria of the strain *E. Coli* XL1-Blue was then transfected with the recombinant phages derived from one of the described phage cDNA libraries, plated at a density of 4-5 x 10^3 pfus (plaque forming units) per plate, and incubated for eight hours at 37°C. A nitrocellulose membrane was then placed on each plate, followed by overnight incubation.

The membrane was subsequently washed four times with TBS containing 0.05% Tween-20, and was immersed afterwards in TBS containing 5% non-fat dried milk. After one hour, the nitrocellulose membranes were washed three times with TBS, followed by the incubation with diluted human serum secured from the

autologous patient. The serum was pretreated, as described in detail by Sahin et al. (1995), U.S. Patent No. 5,698,396 and International Application WO 96/40209, to deplete interfering antibodies directed against antigens derived from *E. Coli* and phages. The stripped human serum was diluted 1:100 in TBS containing 0.5% milk powder (w/v). The membranes were incubated in the human serum overnight with gentle shaking, followed by three washes with TBS. Afterwards, the membranes were incubated with polyclonal goat anti-human IgG Fcγ conjugated with HRP. The conjugated antibodies were diluted 1:2000 in TBS-1% BSA. After incubation for one hour at room temperature, the membranes were washed three times with TBS. The positive clones were visualized using 30% solution of hydrogen peroxidase. Positive clones were further subcloned to monoclonality by repeated rounds of transfection and testing.

At the end of this screening procedure, ten cDNA clones (MEL 1-10) were obtained from the MEL-N1 library; three cDNA clones (Thy 1-3) were obtained from the Thy-N1 library; seven cDNA clones (Thy 5-6, 9, 11-12 and 14-15) were obtained from the Thy-N2 library.

Example 2

Sequencing the isolated cDNA clones.

The insert size of the isolated cDNA clones was determined using restriction enzymes and listed in Table I. The inserts of the cDNA clones were sequenced from the 3' end using standard techniques. See Sambrook et al. (1989), for example. SEQ ID NOS: 1-20 illustrate the sequences of the 3' portions of these isolated cDNA clones. Following nucleotide homology search of the databases, these sequences were resolved into known and unknown sequences. Table 1 summarizes the results. In Table 1, the "+" signs are used to indicate the relative strength of reactivity of each clone toward the corresponding patient serum.

SEQ ID NO: 1 (MEL 1) corresponds to a portion of the partial mRNA sequence for the repressor protein (SEQ ID NO: 21). SEQ ID NO: 2 (MEL 2) corresponds to a portion of the KIAA0201 gene (SEQ ID NO: 22, homologue to heat shock protein HSP). SEQ ID NOS: 4 and 8-10 (MEL 4 and MEL 8-10) correspond to portions of the Ki-67 nuclear antigen gene (SEQ ID NO: 23 and 24). SEQ ID NOS: 5-6 (Mel 5-6) correspond to portions of the CENP-B gene (SEQ ID NO: 25). SEQ ID NO: 3 (MEL 3) is matched by several EST sequences in Genbank. SEQ ID NO: 7 (MEL 7) does not find any sequence match in the databases.

SEQ ID NO: 11 (Thy 1) corresponds to a portion of the TAFII68 (TBP associated factor) gene (SEQ ID NO: 26). SEQ ID NO: 12 (Thy 2) corresponds to a portion of the lipocortin II gene (SEQ ID NO: 27). SEQ ID NO: 13 (Thy 3) corresponds to a portion of the thyroglobulin gene (SEQ ID NO: 28). SEQ ID NO: 16 (Thy 9) corresponds to a portion of the thymosin beta-4 gene

(SEQ ID NO: 29). SEQ ID NO: 17 (Thy 12) corresponds to a portion of the Acid ceramidase gene (SEQ ID NO: 30). SEQ ID NOS: 14,17 and 19-20 (Thy 5, Thy 11, Thy 14 and Thy 15) are only matched by EST sequences in the databases.

Table II

SEQ ID NO	Clone	Serum react	Insert size (kb)	Access. No.	Identity
1	Mel 1	++	0.4	D30612	mRNA (partial) for repressor protein
2	Mel 2	+++++	0.7	D86956	KIAA0201, homolog to HSP
3	Mel 3	+	1.65	Novel	EST matches
4	Mel 4	++++	0.9	X65551/50	Ki-67 nuclear antigen, LONY-BR-8 (Breast SEREX)
8	Mel 8	+++	0.8		
9	Mel 9	++++	0.9		
10	Mel 10	++++	1.0		
5	Mel 5	++	1.25	X55039	CENP-B centromere autoantigen
6	Mel 6	+++	1.2		
7	Mel 7	+++	0.9	Novel	No EST match
11	Thy 1	+	0.8	X98893	TAF 1168
12	Thy 2	+	1.2	D000617	lipocortin II
13	Thy 3	+	1.7	X05615	thyroglobulin
14	Thy 5	+	2.7	Novel	Novel-EST matches
15	Thy 6	++	3.4	Novel	Novel-ESTs
16	Thy 9	+	0.6	M17733	thymosin beta-4
17	Thy 11	+	4.2	Novel	Novel-EST matches
18	Thy 12	++	0.8	U70063	Acid ceramidase
19	Thy 14	++	2.9	Novel	Novel-EST matches
20	Thy 15	++	2.5	Novel	Novel-EST matches

Table III

SEQ ID NO.	Accession NO.	Identity
21	D30612	Homo sapiens mRNA for repressor protein, partial cds
22	D86956	Human mRNA for KIAA0201 gene, complete cds
23	X65550	H.sapiens mki67a mRNA (long type) for antigen of monoclonal antibody Ki-67
24	X65551	H.sapiens mki67a mRNA (short type) for antigen of monoclonal antibody Ki-67
25	X55039	Human hCENP-B gene for centromere autoantigen B (CENP-B)
26	X98893	H.sapiens mRNA for TBP associated factor (TAFII68)
27	D00017	Homo sapiens mRNA for lipocortin II, complete cds
28	X05615	Human mRNA for thyroglobulin
29	M17733	Human thymosin beta-4 mRNA, complete cds
30	U70063	Human acid ceramidase mRNA, complete cds

Example 3

Clone Reactivity with
Sera from Allogeneic Cancer Patients

The SEREX clones were tested for reactivity with 52 allogeneic sera from cancer patients (7 rectal, 13 lung,21 breast, 11 colon) and 10 allogeneic sera from normal individuals. The procedure was essentially as the SEREX method described in Example 1, except that 'defined' cDNA molecules, i.e., the isolated clones were being expressed, blotted and screened with allogeneic sera rather than autologous sera. The allogeneic sera were treated in the same way the autologous sera were treated which as described in Example 1. Briefly, XL-1 E Coli cells were grown to OD 1.0, spun down and suspended in 10 ml $MgSO4$. 20 ml of primary phage stock in SM-buffer were added to 100 ml of bacterial solution. Phage was sorbed for 15 min at 28°C, then 0.5 ml of 2 YT medium and IPTG were added and samples were incubated at 42°C until lysis (6-7 hrs). Afterwards, cell debris was spun down and 2 ml solution were transferred to Hybond-C filters, incubated with allogeneic sera samples overnight (sera 1:100) and developed by standard method with anti-human anti-IgG horse radish peroxidase conjugate, stained with DAB. The level of immunoreactivity was estimated in arbitrary units, where 4=high signal level, 3=medium signal level, 2=weak signal, 1= absence of signal. An average mean of signals for each clone and tye of cancer have been calculated, and mean of average signal for normal sera have been subtracted. Table IV summarizes the results.

Table IV Dot Blot Analysis

	CLONES																			
ID NO	1	2	3	5	6	9	11	12	14	15	16	17	18	19	20	21	22	23	24	25
Rectal cancer																				
Rec1	1	2	1	4	3	1	1	2	1	2	2	3	3	3	2	2	2	2	2	2
Rec8	1	3	3	3	3	3	3	3	2	2	3	2	2	3	3	2	2	3	3	3
Rec3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	3	3	3
Rec4	2	2	3	3	3	2	3	3	3	2	3	2	2	2	2	2	2	3	3	3
Rec5	4	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	3
Rec6	4	2	3	3	3	3	3	3	3	2	2	3	2	2	2	2	2	2	2	3
Rec2	3	2	3	3	3	2	3	3	3	3	3	4	3	3	3	2	2	2	3	3
	18	16	18	21	20	16	18	19	17	16	18	20	17	18	16	14	14	17	18	20
Lung cancer																				
Lu2	1	3	3	3	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3	3
Lu3	1	3	3	4	3	3	3	3	3	1	2	2	2	2	2	2	2	3	3	3
Lu46	1	2	3	3	3	2	1	1	1	3	2	3	3	3	3	3	3	2	2	4
Lu18	3	2	3	4	3	3	3	3	2	2	2	2	2	2	2	2	2	3	3	3
Lu24	1	1	1	3	3	3	3	2	2	3	2	2	2	3	3	3	2	3	3	4
Lu26	3	2	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Lu40	1	3	3	3	3	2	3	3	1	2	2	2	2	3	3	2	2	3	3	4
Lu44	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	3	4
Lu17	1	3	3	3	3	2	2	3	2	3	3	2	2	3	3	3	1	3	3	4
Lu49	3	2	2	3	3	2	3	3	3	2	2	3	2	3	3	3	3	2	2	3
Lu4	2	2	2	3	3	2	2	3	2	1	2	3	1	2	2	2	2	2	2	3
Lu47	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Lu50	2	1	1	3	3	1	1	2	2	1	2	2	3	3	3	3	1	2	2	2
	22	30	33	41	39	31	32	34	29	29	30	32	30	35	34	34	28	33	34	42
Breast cancer																				
Br2	3	2	1	3	2	3	2	2	3	3	2	2	3	2	2	2	2	2	2	3
Br15	4	2	3	3	3	3	3	3	3	2	4	2	4	3	2	2	2	3	3	4
Br8	4	1	1	2	2	1	2	2	3	1	1	3	3	2	2	2	2	1	1	3
Br1	3	1	2	2	2	2	1	3	1	2	2	3	3	2	2	1	1	2	1	2
Br9	2	2	2	2	3	3	3	3	1	3	2	3	2	2	2	2	2	1	2	1
Br3	2	1	3	2	3	3	3	2	2	2	1	3	2	2	2	2	2	2	3	3
Br10	3	2	4	3	3	3	1	4	2	2	3	4	4	3	3	3	2	2	2	2
Br17	3	3	3	3	3	2	3	3	3	2	3	3	3	3	3	1	1	3	3	3
Br16	1	1	1	1	2	2	1	2	1	2	1	1	1	1	1	1	1	1	2	1
Br4	2	2	2	1	2	2	2	2	1	1	1	2	2	2	2	1	1	1	1	2
Br6	3	2	2	1	2	1	2	2	1	2	2	2	2	2	2	2	2	2	2	3
Br14	2	2	1	1	4	3	3	3	2	2	1	3	3	3	3	3	2	2	3	3
Br5	3	3	3	2	4	3	3	3	2	2	2	3	3	3	3	3	1	1	2	3
Br20	1	2	2	2	2	2	2	2	1	2	2	1	2	2	1	2	1	1	1	2
Br12	3	1	3	2	3	3	2	3	3	3	3	3	3	2	2	2	3	2	2	3
Br19	3	3	3	2	3	3	2	3	2	2	2	3	3	1	3	3	1	1	1	2
Br18	3	3	3	2	3	3	2	2	1	1	2	2	2	2	2	3	1	1	1	3
Br11	2	1	2	1	3	2	2	2	1	1	2	2	2	2	2	2	2	1	1	2
Br248	1	1	2	2	2	2	3	2	4	2	3	3	2	3	3	1	1	3	3	4
Br257	1	2	3	3	3	3	3	3	4	1	3	2	3	4	4	3	3	3	4	4
Br263	1	2	2	3	3	2	4	3	4	2	2	1	2	2	2	1	1	2	3	3
	50	39	48	43	57	51	49	54	45	40	44	51	54	48	48	42	34	37	43	56
Colon cancer																				
Co5	4	3	3	3	3	3	3	3	3	2	2	3	3	3	3	3	1	3	3	3
Co30	3	2	3	3	3	3	3	3	3	2	2	3	3	3	3	3	2	3	3	3
Co17(?)	4	2	3	3	3	3	3	3	3	2	3	3	3	3	3	2	2	3	3	3
Co37	3	1	2	2	2	2	2	2	2	2	2	3	3	2	2	2	1	1	2	2
Co33	3	3	3	3	3	3	3	3	3	2	2	3	3	2	2	2	2	2	2	3

Co4	4	2	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	3	3	3
Co34	3	2	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	3	3	3
Co36	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	3	3	3
Co2	2	2	2	2	3	3	2	2	2	2	3	3	3	3	3	1	1	2	2	3
Co3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	2	3	3	3
Co32	3	3	3	3	3	3	3	3	1	2	2	3	2	2	2	1	1	3	3	3
	35	26	31	31	32	32	31	31	29	26	28	33	32	29	29	22	18	29	30	32
	CLONES																			
ID	1	2	3	5	6	9	11	12	14	15	16	17	18	19	20	21	22	23	24	25
Normal sera																				
No10	3	1	1	2	1	2	2	1	2	2	3	3	2	3	2	2	2	2	2	2
No8	1	1	3	2	2	2	2	2	2											
No5	1	2	2	3	1	1	3	2	2	1	1	2	2	1	2	2	3	1	2	2
No22	2	2	2	1	2	2	3	3	1	3	2	2	2	1	4	1	3	1	2	2
No13	1	1	2	2	1	2	3	2	1	1	1	1	1	1	2	1	2	1	1	1
No3	1	2	3	2	1	2	2	1	1	1	1	2	3	2	3	2	3	1	2	2
No21	1	2	3	3	2	2	2	2	2	1	1	2	2	1	3	2	2	1	2	2
No1	2	2	2	1	1	2	2	2	2	1	1	1	3	1	2	1	2	1	1	1
No2	1	1	2	1	1	1	1	1	1	1	1	2	3	1	1	2	2	1	2	2
No15	2	2	1	1	1	1	1	1	1	1	1	2	3	1	2	1	2	1	1	1
	15	16	21	18	13	17	21	17	15	12	12	17	21	12	21	14	21	10	15	15

All sera scoring 4 or 3 were classed as positive and the results of the dot blotting were summarized in Table V.

Table V Clone Reactivity with Allogenic Sera

ID	Clone	SEQ ID NO	Allogenic cancer sera				
			Rectal (n=7)	Lung (n=13)	Breast (n=21)	Colon (n=11)	Normal (n=10)
1	Thy1	11	4	3	11	10	1
2	Thy2	12	2	6	4	5	0
3	Thy3	13	5	9	9	9	9
5	Thy5	14	6	13	6	9	2
6	Thy6	15	6	13	13	10	0
9	Thy9	16	3	6	11	10	0
11	Thy11	17	5	8	9	9	3
12	Thy12	18	5	9	11	9	1
14	Thy14	19	4	5	8	8	0
15	Thy15	20	2	6	3	4	1
16	Mel1	1	4	4	6	6	1
17	Mel2	2	5	6	11	11	1
18	Mel3	3	3	5	11	10	4
19	Mel4	4	4	9	7	7	1
20	Mel5	5	2	8	7	7	3
21	Mel6	6	0	8	6	2	0
22	Mel7	7	0	4	2	0	3
23	Mel8	8	3	7	4	8	0
24	Mel9	9	4	8	7	8	0
25	Mel10	10	6	11	13	10	0

Based on the data in Table V, the mean of the intensity values for each cancer sera type was calculated for each clone. The mean of the intensity values for each normal sera type was calculated For each clone. The difference between the cancer sera and normal sera is presented in Table VI. A value over 1.0 indicates a specific recognition of the clone by the type of cancer sera.

So for instance, SEQ ID No's 4, 8, 9, 10, which represent sequences of Ki-67, are specifically recognized by serum antibodies from rectal, lung, breast and colon cancer patients. Ki-67 is a marker of proliferation used in immunohistochemistry. The present invention has shown for the first time the association of this antigen with cancer.

Table VI Specific Clone reactivity with allogenic cancer sera

ID	Clone	SEQ ID NO	Allogenic cancer sera Rectal (n=7)	Lung (n=13)	Breast (n=21)	Colon (n=11)
1	Thy1	11	1.07	0.19	0.88	1.68
2	Thy2	12	0.69	0.71	0.26	0.76
3	Thy3	13	0.47	0.44	0.19	0.72
5	Thy5	14	1.2	1.35	0.24	1.02
6	Thy6	15	1.55	1.7	1.41	1.61
9	Thy9	16	0.59	0.68	0.73	1.21
11	Thy11	17	0.47	0.36	0.23	0.72
12	Thy12	18	1.01	0.92	0.87	1.12
14	Thy14	19	0.92	0.73	0.64	1.14
15	Thy15	20	1.09	1.03	0.7	1.16
16	Mel1	1	1.37	1.11	0.9	1.35
17	Mel2	2	1.16	0.76	0.73	1.3
18	Mel3	3	0.32	0.21	0.47	0.81
19	Mel4	4	1.37	1.49	1.09	1.44
20	Mel5	5	0.91	0.52	0.19	0.54
21	Mel6	6	0.6	1.22	0.6	0.6
22	Mel7	7	0	0.05	0	0
23	Mel8	8	1.42	1.54	0.76	1.64
24	Mel9	9	1.07	1.12	0.54	1.23
25	Mel10	10	1.36	1.73	1.17	1.41

Example 3

Reactivity of a Fragment of Ki67 Recombinantly Expressed in Bacteria With Allogenic Sera from Cancer Patients

A 0.5 kB sequence of Mel-9 clone was amplified by PCR, using Vent polymerase and a pair of specific primers. The primers used are:

Oligo N1, Ki67 sense, Nhe, 6His, 5610
ATTGCTAGCCACCACCACCACCACCACAAACTGGACCCAGCAGCAAGTGTAAC
(SEQ ID NO:31); and
Oligo N2, Ki67 antisense, EcoRI, 6420
CGGGAATTCCTATAGAGCCTCAGCCTTTTCCTTAGG (SEQ ID NO: 32)

Amplified cDNA fragment of Ki67 was subcloned into pET23d in a correct reading frame with the His-tag epitope. Expression of recombinant His-tag/Ki67 was carried out in DE3 pLysS cells in the presence of 1 mM IPTG. Recombinant protein had a predicted molecular weight (about 21 kDa) and was purified nearly to homogeneity by affinity chromatography on Talon Sepharose. Purified His-tag/Ki67 was used for heterologous screening of sera from healthy individuals and cancer patients.

Highly purified recombinant Ki67 was coupled to 96-well immunoassay plates (0.1-1 mkg per well). Non-specific binding of sera's IgG to plates was blocked by BSA. Binding of recombinant Ki-67 by specific antibodies present in normal and cancer sera was measured by ELISA using standard techniques. Four experiments were done. In each experiment, each sample of normal or cancer sera was tested against recombinant Ki-67. The mean values for corresponding sera types were calculated in each experiment and averages for normal and cancer sera were compared to determine differences. The difference in the measured intensity reflects the

difference in the amount of specific antibodies between cancer and normal sera.

Table VII presents the results. The results of this study indicate that sera from lung and breast cancer patients show increased immunoreactivity towards recombinant Ki67. The differences between the cancer sera and normal sera in immunoreactivity towards recombinant Ki67 were considered valid if p-value was less than 0.05. Statistical analysis indicated that significant differences were seen with lung and breast cancer sera, indicating that these cancer seras contained greater amounts of Ki-67 specific antibodies compared to normal sera.

Table VII

ELIZA: Recombinant Ki-67 screened with allogenic cancer and normal sera

Exp	Sera Compared	Difference	Statistically Significant
exp 1	N1 vs. LU1	+	Yes
exp 1	N1 vs. BR1	+	Yes
exp 1	N1 vs. THY1	+	No
exp 2	N2 vs. LU2	+	Yes
exp 2	N2 vs. CO2	+	No
exp 3	N3 vs. LU3	+	Yes
exp 3	N3 vs. BR3	+	Yes
exp 3	N3 vs. THY3	+	No
exp 4	N4 vs. LU4	+	Yes
exp 4	N4 vs. BR4	+	Yes

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule or a part thereof, wherein said nucleic acid molecule has a sequence as set forth in any one of SEQ ID NOS: 3, 7, 14, 17, 19 or 20.

2. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 3.

3. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 7.

4. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 14.

5. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 15.

6. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 17.

7. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO: 19.

8. The isolated nucleic acid molecule or a part thereof of claim 1, wherein said nucleic acid molecule has a sequence as set forth in SEQ ID NO; 20.

9. An isolated nucleic acid molecule comprising a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to at least one nucleic acid molecule of SEQ ID NOS: 3, 7, 14-15, 17 or 19-20.

10. An isolated protein encoded by the isolated nucleic acid molecule or a part thereof of claim 1.

11. An isolated antibody specific for a protein encoded by the nucleic acid molecule or a part thereof of claim 1.

12. An expression vector comprising the nucleic acid molecule or a part thereof of claim 1, operably linked to a promoter to effect the expression of a protein encoded by said nucleic acid molecule or a part thereof.

13. A cell, transformed or tranfected with the isolated nucleic acid molecule or a part thereof of claim 1.

14. A cell, transformed or tranfected with the expression vector of claim 12.

15. The cell of claim 14, wherein said cell is an antigen presenting cell having on the surface, a complex of an MHC molecule and a peptide, said peptide being encoded by a fragment of said nucleic acid molecule.

16. An isolated peptide/HLA complex, wherein said peptide is encoded by a fragment of any one of SEQ ID NOS: 3, 7, 14-15, 17 or 19-20.

17. A method for diagnosing a pathological condition in a patient, wherein said condition is characterized by an abnormal expression of at least one nucleic acid molecule of SEQ ID NOS: 21-30 or a nucleic acid sequence comprising any one of SEQ ID NO: 3, 7, 14-15, 17 or 19-20, said method comprising the steps of:

(i) obtaining a sample from said patient;

(ii) assessing the expression of said nucleic acid olecule in said sample; and

(iii) determining the expression of said nucleic acid molecule as abnormal thereby diagnosing said pathological condition.

18. The method of claim 17, wherein said pathological condition is selected from the group consisting of melanoma, the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer and colon cancer.

19. The method of Claim 18, wherein said pathological condition is melanoma and wherein said nucleic acid molecule is any one of SEQ ID NO: 21-25, or a nucleic acid sequence comprising SEQ ID NO: 3 or 7.

20. The method of Claim 18, wherein said pathological condition is characterized by the presence of a thyroid tumor and wherein said nucleic acid molecule is any one of SEQ ID NOS: 26-30, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15, 17 or 19-20.

21. The method of Claim 18, wherein said pathological condition is rectal cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS:

21-24, 26 or 30, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

22. The method of Claim 18, wherein said pathological condition is lung cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21 or 23-25, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

23. The method of Claim 18, wherein said pathological condition is breast cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 23-24, or a nucleotide sequence comprising SEQ ID NO: 15.

24. The method of Claim 18, wherein said pathological condition is colon cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-24, 26 or 29-30, or a nucleotide sequence comprising SEQ ID NO: 14-15 or 19-20.

25. The method of claim 18, wherein the expression of said nucleic acid molecule is assessed by assaying the level of mRNA of said nucleic acid molecule.

26. The method of claim 18, wherein the expression of said nucleic acid molecule is assessed by assaying the level of a protein encoded by said nucleic acid molecule or parts thereof.

27. The method of claim 18, wherein the expression of said nucleic acid molecule is assessed by assaying the level of an antibody in the serum that is specific for a protein encoded by said nucleic acid molecule or parts thereof.

28. The method of claim 18, wherein the expression of said nucleic acid molecule is assessed by assaying a cell expressing an MHC/peptide complex and wherein said peptide is encoded by a fragment of said nucleic acid molecule.

29. A composition comprising a carrier and an antisense DNA of a nucleic acid molecule or a part thereof, wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-30, or a nucleic acid sequence comprising any one of SEQ ID NO: 3, 7, 14-15, 17 or 19-20.

30. A composition comprising a carrier and a protein encoded by a nucleic acid molecule or a part thereof, wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-30, or a nucleic acid sequence comprising any one of SEQ ID NO: 3, 7, 14-15, 17 or 19-20.

31. A composition comprising a carrier and an antibody directed against a protein encoded by a nucleic acid molecule or a part thereof, wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-30, or a nucleic acid sequence comprising any one of SEQ ID NO: 3, 7, 14-15, 17 or 19-20.

32. A composition comprising an immunogenic cell and a carrier, wherein said cell expresses a peptide complexed with an MHC molecule, said peptide being encoded by a fragment of a nucleic acid molecule, and wherein said nucleic acid molecule is any one of SEQ ID NOS: 14-15, 17 or 19-20.

33. A method for treating a patient afflicted with a pathological condition, wherein said

condition is characterized by an abnormal expression of at least one nucleic acid molecule of SEQ ID NOS: 21-30 or a nucleic acid sequence comprising any one of SEQ ID NO: 3, 7, 14-15, 17 or 19-20; said method comprising administering to said patient a therapeutically effective amount of at least one of: an antisense DNA of said nucleic acid molecule or part thereof, a protein encoded by said nucleic acid molecule or part thereof, an antibody specific for a protein encoded by said nucleic acid molecule or part thereof, or a cell expressing a MHC/peptide complex wherein said peptide is encoded by a fragment of said nucleic acid molecule.

34. The method of claim 33, wherein said pathological condition is selected from the group consisting of melanoma, the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer and colon cancer.

35. The method of claim 34, wherein said pathological condition is melanoma and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-25, or a nucleic acid sequence comprising SEQ ID NO: 3 or 7.

36. The method of claim 34, wherein said pathological condition is characterized by the presence of a thyroid tumor and wherein said nucleic acid molecule is any one of SEQ ID NOS: 26-30, or a nucleic acid sequence comprising any one of SEQ ID NOS: 14-15, 17 or 19-20.

37. The method of Claim 34, wherein said pathological condition is rectal cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS:

21-24, 26 or 30, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

38. The method of Claim 34, wherein said pathological condition is lung cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21 or 23-25, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

39. The method of Claim 34, wherein said pathological condition is breast cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 23-24, or a nucleotide sequence comprising SEQ ID NO: 15.

40. The method of Claim 34, wherein said pathological condition is colon cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-24, 26 or 29-30, or a nucleotide sequence comprising SEQ ID NO: 14-15 or 19-20.

41. A method for treating a subject afflicted with a pathological condition, wherein said condition is characterized by an abnormal expression of at least one nucleic acid molecule of SEQ ID NOS: 21-30 or a nucleic acid sequence comprising SEQ ID NO: 3, 7, 14-15, 17 or 19-20, said method comprising:

(i) removing an immuno-reactive cell containing sample from said subject,

(ii) contacting the immuno-reactive cell containing sample with immunogenic cells expressing a peptide encoded by a fragment of said nucleic acid molecule complexed with an MHC molecule;

(iii) selecting the cytolytic T cells that are specific for said peptide; and

(iv) introducing a therapeutic effective amount of the cytolytic T cells produced from step (iii) to said subject thereby alleviating said condition.

42. The method of claim 41, wherein said pathological condition is one selected from the group consisting of melanoma, the presence of a thyroid tumor, rectal cancer, lung cancer, breast cancer and colon cancer.

43. The method of claim 42, wherein said pathological condition is melanoma and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-25, or a nucleic acid sequence comprising SEQ ID NO: 3 or 7.

44. The method of claim 42, wherein said pathological condition is characterized by the presence of a thyroid tumor and wherein said nucleic acid molecule is any one of SEQ ID NOS: 26-30, or a nucleic acid sequence comprising any one of SEQ ID NOS: 14-15, 17 or 19-20.

45. The method of Claim 42, wherein said pathological condition is rectal cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-24, 26 or 30, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

46. The method of Claim 42, wherein said pathological condition is lung cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21 or 23-25, or a nucleotide sequence comprising any one of SEQ ID NOs: 14-15 or 20.

47. The method of Claim 42, wherein said pathological condition is breast cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 23-24, or a nucleotide sequence comprising SEQ ID NO: 15.

48. The method of Claim 42, wherein said pathological condition is colon cancer and wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-24, 26 or 29-30, or a nucleotide sequence comprising SEQ ID NO: 14-15 or 19-20.

49. A method of identifying the association of a pathological condition with an abnormal expression of a nucleic acid molecule, wherein said nucleic acid molecule is any one of SEQ ID NOS: 21-30 or a nucleic acid sequence comprising SEQ ID NO: 3, 7, 14-15, 17 or 19-20, said method comprising:

obtaining the serum from a patient suffering said pathological condition; and

detecting the presence of an antibody in said serum specific for an antigen encoded by said nucleic acid molecule, as indicative of an association of said pathological condition with the abnormal expression of said nucleic acid molecule.

50. The method of claim 49, wherein said nucleic acid molecule is SEQ ID NO: 23 or 24.

51. The method of claim 49, wherein said pathological condition is a cancer.

52. The method of claim 49, wherein the detection is carried out using a SEREX screening assay.

SEQ ID NO: 1 (Mel1)

TGTNCAANGGGGGNTNAGTGGTNACNGNCATGGGTCACNNGCCTNTTCCC
NNNGCNCCNGNNATATTGNGTGCANGNCGCANTNTTTNGNANANGCAGCN
ACNGTGGACTGGTCCCTCNACAGGCCAGTTTNNNGGCCCCCAGAGTCANG
NCCTCNACCANTGANNGATTNTGTTCCNGTTCATCCNCAGNGNAGAAGGG
GCGAGGGAGAGNCNTTNTGCTTTTGAGGGTNANCNGTNAGGNGTNTNTTC
CCNGCAGCAGCCGGTCAAGTGGATANTAGNGTNTGNGCNTCNGGNTNTCG
TGCNNTGGGCCTCCCAATTGGNGGTATNTGNACTGCCCGTGNTCANGGAC
NTGGCTACAGACCNTGNTGNGGCCANACCNTGCAGGCGCCTCGGGAAGCG
CCCAAAGGATTCCCCTNNANGTTGGTGCACNTGATCCATAGNTCCGGGCG
CTGNGTCCCGNGGGGCCACAGTNNCCATNTCAGCGTCTTGCATGGCNTGG
CACCGGGTGGGGTGGTATGCCCCAGGACCCNTGNTTGTGNCAAAAATGAC
TTTCCNTGCCCTTGCCGTGGGGCCGGGGTTCCTCCCANCCGGGATCACAG
TGGGCAGCCGGCACCCGGCACCACTTTGGCGNGCGTCCTGCTTCCGCCCT
CGCCCTCATNTACGNTGNNCCGCTTTCCTCNGACCCCTTTTTNCCGTGCA
AAGGAATTNTTGACATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAANAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAA

SEQ ID NO: 2 (Mel2)

CTCCGGGAAGCGGCTCCCATTTGTTGTTNGTACCCCGGGAATTCGGCACG
AGGAGTTCAGANGACAAGCTGTGTGGACCATATGAAAAATTTATATGTGA
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CTGTATGAAGAAGGAGAGGACCCAAGCTAAACAAGCATATGTTGACAAGT
TGGAAGAATTAATGAAAATTGGCACTCCAGTTAAAGTTCGGTTTCAGGAA
GCTGAAGAACGGCCAAAAATGTTTGAAGAACTAGGACAGAGGCTGCAGCA
TTATGCCAAGATAGCAGCTGACTTCAGAAATAAGGATGAGAAATACANCC
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TCAGGATCCAGTTGTACGTGCTCAGGAAATTAAAACAAAAATCAAGGAAT
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SEQ ID NO: 3 (Mel3)

TGGGNTTTTTCCCCCTTTTTTNGNAACCCCNTTTTCNTNCCCCCNNTTTG
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NGGTTTCCCAACCGTGCCCCNCCGTGGGTNACCCCCCGGNGGCNNCCAGG
GGTNGGCCNTGGGGGTTTCCGGCCGGGGGGTGCCTTTTCCCNTTNNCANN
CNAGTNAGGNTTTTTNTNGGGGGGCCCCCAANCCCTTTTTGGGAGGGGTC
CCGNNGNAGGTCCCNCNTTGGCCCCCTNCAAGGGTNGGNGCCCCCNCCCC
CACCCCCCCGGNCCCCTTTGGGAGNCCCGTTTTAATCNNTNGGGGGTCNT
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GGGGCCCCCCCCCCTNGGAGTTNCCCAGGGGGGTTCCNTTTNGGNCNNTN
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GGGGCCTTGGGGTTGGCCCCGGGNCCCCCCNNCCCGNTNNNCCNTTNCCC
NNTTNGTTTNNATNAANTTTNCCCNTCCCCCTTTTTNGGGGNNGACNTTT
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A

SEQ ID NO: 4 (Mel4)

TTGTGTTGGAATTNTTGAGCGGATTAACANTTTTNACACNGGNAAACAGN
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TCACACAGGAAACAGCTATGACCATGATTACGCCAAGCTCCGAGATCTGG
ACGAGCTTTTTTTTTTTTCTCGGGAAGCGCGCCATTGTGTTGGTACCCG
GGAATTCGGCACGAGGCAAAACAGAAACTGGACCCAGCAGCAAGTGTAAC
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AAGACTTGGCTGGCTTGAAAGAGCTCTTCCAGACACCAATATGCACTGAC
AAGCCCACGACTCATGAGAAAACTACCAAAATAGCCTGCAGATCTCCACA
ACCAGACCCAGTGGGTACCCCAACAATCTTCAAGCCACAGTCCAAGAGAA
GTCTCAGGAAAGCAGACGTAGAGGAAGAATCCTTAGCACTCAGGAAACGA
ACACCATCAGTAGGGAAAGCTATGGACACACCCAAACCAGCAGGAGGTGA
TGAGAAAGACATGAAAGCATTTATGGGAACTCCAGTGCAGAAATTGGACC
TGCCAGGAAATTTACCTGGCAGCAAAAGATGGCCACAAACTCCTAAGGAA
AAGGCCCAGGC

SEQ ID NO: 5 (Mel5)

ACCCCCAGGGGCAGGGGGAATTTTTTTGGGAAACCCGTTTNTGCATGGAG
CCCAGNATTGNAGGGCCCCCANATCCCTTTNAGTAATTGNTTTCCCCTTG
GTCCTTGNAAACAGGCCCCGGTTNACTTTGGCCGGGGCCCNGGGGGTTGA
GTTCAGCCTTNANTTGCCTTGTTAATTGCNTCTTTTTTCAGAATCCTCTT
TCTTCCCAATTTGNCCTTGGGTTCAGGGGACCAGTTGGGGCGGNTGGGGA
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GCCATCCACGTCAGGTCTTTGGTGGGGGACCCCAAAGCCATTTTGGGAA
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CACCCCCACCCCCCAGGCCGCCTTGAGAAGCACAGTTTAACTCANTGCGG
GCTCNTGAGCCTGCTTCTGCCTGCTTTCCACNTCCCCAGTCCCTTTCTNT
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CAGNTGCAGGCCCCATGCCTNTCCTCCCTCTNTGGCAGGGCCCCATCNTG
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SEQ ID NO: 6 (Mel6)

TTTGAACATAAAAGGTTGNGTCANTTGAACNTAGTTNTGCCCCCAAACCT
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CCCTTGNTCTTGAACAGGCCCCGGTAACTTCGGCCGGGCCCGGGGNTGAG
GTCAGCCTCATTGCNTGCTTATTGCNTCTTTCTCAGAATCCTCTTTCNTC
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GGATGGGCCCTGGAGGTTCCCGGCCGGAGAGTGCCTCTCCCCTCTGCCAT
CCACGTCAGGTCTTTGGTGGGGGGACCCCAAAGCCATTCTGGGAAGGGCT
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CCACCCCNCAGGCCGCCTTGAGAAGCACAGTTTAACTCACTGCGGGCTCC
TGAGCCTGCTTCTGCCTGCTTTCCACCTCCCCAGTCCCTTTCTCTGGCCC
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GCAGGCCCCATGCCTCTCCTCCCTCTCTGGCAGGGCCCCATCCTGGGCAG
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TTAACAGCCAAAAAAAAAAAAAAAAAAA

SEQ ID NO: 7 (Mel7)

CCCCNNNTCCCTNGNACNTNGGNCNTTTTNTTGGAAATTNGGGGGGGCNT
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NTCGTTTTNNCGNNCTCNGTTTNTTTTTTTGGGGGGGGNTTTCTNTTTGG
GGGNCCTGTTNACCCCGGTTTTNGGGGGCCCNTGGTNTTCTTNTTTCCCT
NGTTNNGGGGGGACCCGTNCCCCTTTTCNCCNNTTGNGACCNGGGTNGCG
GGGCCCNCNTNNNCTCNNATTGGGACNNAANTTNGNTCNNTTTGTNCCCG
GGGGNNCCCCCNCCGGGCNGGGGGGGGTTTNGGGTTTTTTGNNTCNAAGN
TNGGTNCCTTNGGCCNGGGTTTNCCCCCNNCCTTGNTTTGGGGNCCCCCC
CCCGGGGGGGGGGCTTTTTNGGNNCCCCNTTTNNTTNGNNCCCGGGTNNN
GGGCCCCCAATCCNTTTGGNATGGTTNCCCTNGTCCTTGAANCGGNCCNG
TNNCCTNGGCCGGGCCCNGGGNTTGGGTTTGGGGTTTCCCNGGGGCCCCC
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AAAAA

SEQ ID NO: 8 (Mel8)

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AACACCTTAGGGANGAGGGCCCAATTCACTNGAAGACCTTGCCCGGNTTC
AAAGGAGTTNTTCCAGACACCGGACCCACATTGAGGAATCAACAACTGAT
GACAAAACTACCAAAACAGCNTGCAAATCTTCCACCACCCAGAATCAATG
GACACTCCAACAAGCACAAGAGGCGGCCCAAAACACCTTTGGGGAAAAGG
GATATAGTGGAAGAGCTCTCAGCCCTGAAGCAGCTCACACAGACCACACA
CACAGACAAAGTACCAGGAGATGAGGATAAGGCATCAACGTGTTCAGGGA
AACTGCAAAACAGAAACTGGACCCAGCAGCAAGTGTAACTGGTAGCAAGA
GGCAGCCAAGAACTCCTAAGGGAAAAGCCCAACCCCTAGAAGACTTGGCT
GGCTTGAAAGAGCTCTTCCAGACACCAATATGCACTGACAAGCCCACGAC
TCATGAGAAAACTACCAAAATAGCCTGCAGATCTCCACAACCAGACCCAG
TGGGTACCCCAACAATCTTCAAGCCACAGTCCAAGAGAAGTCTCAGGAAA
GCAGACGTAGAGGAAGAATCCTTAGCACTCAGGAAACGAACACCATCAGT
AGGGAAAGCTATGGACACACCCAAACCAGCAGGAGGTGATGAGAAAGACA
TGAAAGCATTTATGGGAACTCCAGTGCAGAAATTGGACCTGCCAGGAAAT
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SEQ ID NO:9 (Mel9)

TTTTGGGCACCCCCAGGGTTTTAANANNTTTATTGNTTNCCGGGNTTNGT
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GGAAACAGGTNTTGNCCNATTGATTACNCCCAAGGTTATTTNGGTTGAC
AATTATTGANTACTTCAAGTTNNCTNTTAGCTTTACATTGCAAAGGGTGT
CGGCNTAAGCCGAAGATATCGGGTNGAGTTATATTGAGCAGAATCCCCCC
GTTGAAGGATTTAACCGTGTTATCTNGNTGGAATATTCATGGCGTATTTT
TGGATGATAACGAGGCGCAAAAANTGAAAAGTACTTCTTGCAATTGTGAG
CGGACAACAATTTCACACAGGAAACAGCTATGACCATGATTACGCCAAGC
TCCGAGATCTGGACGAGCTTTTTTTTTTTTTCTCGGGAAGCGCGCCATTG
TGTTGGTACCCGGGAATTCGGCACGAGGAAAGACATCAACACATTTGTGG
GGACTCCAGTGGAGAAACTGGACCCAGCAGCAAGTGTAACTGGTAGCAAG
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TGGCTTGAAAGAGCTCTTCCAGACACCAATATGCACTGACAAGCCCACGA
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GTGGGTACCCCAACAATCTTCAAGCCACAGTCCAAGAGAAGTCTCAGGAA
AGCAGACGTAGAGGAAGAATCCTTAGCACTCAGGAAACGAACACCATCAG
TAGGGAAAGCTATGGACACACCCAAACCAGCAGGAGGTGATGAGAAAGAC
ATGAAAGCATTTATGGGAACTCCAGTGCAGAAATTGGACCTGCCAGGAAA
TTTACCTGGCAGCAAAAGATGGCCACAAACTCCTAAGGAAAAGGCCCAGG

SEQ ID NO: 10 (Mel10)

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GCCAGGNGATTGGAAAGGGGCNTTCAAAGGCGTTTTAAGGAATCTTGCAA
AGCCGGATGTTGGACCCCAGCAAANTATTGGAANTGGGATTGAGAGGTTG
GCCCAAGAACACNTAAGGAAGAGGCCCCAATCANTAGANGACCTTGCCGG
CTTCAAAGAGCTNTTCCAGACACCAGGACCACATTGAGGAATCAACAACT
TGATGACAAAACTACCAAAACAGCNTGCAAATCTCCACCACCAGAATCAA
TGGACACTCCAACAAGCACAAGGAGGCGGCCCAAAACACCTTTGGGGAAA
AGGGATATAGTGGAAGAGCTCTCAGCCCTGAAGCAGCTCACACAGACCAC
ACACACAGACAAAGTACCAGGAGATGAGGATAAAGGCATCAACGTGTTCA
GGGAAACTGCAAAACAGAAACTGGACCCAGCAGCAAGTGTAACTGGTAGC
AAGAGGCAGCCAAGAACTCCTAAGGGAAAAGCCCAACCCCTAGAAGACTT
GGCTGGCTTGAAAGAGCTCTTCCAGACACCAATATGCACTGACAAGCCCA
CGACTCATGAGAAAACTACCAAAATAGCCTGCAGATCTCCACAACCAGAC

CCAGTGGGTACCCCAACAATCTTCAAGCCACAGTCCAAGAGAAGTCTCAG
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CAGTAGGGAAAGCTATGGACACACCCAAACCAGCAGGAGGTGATGAGAAA
GACATGAAAGCATTTATGGGAACTCCAGTGCAGAAATTGGACCTGCCAGG
AAATTTACCTGGCAGCAAAAGATGGCCACAAACTCCTAAGGAAAAGGCCC
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SEQ ID NO: 11 (Thy1)

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TGCTNTAGCTTTACATCGCAAGGGTGTCGGCATAAGCCGAAGNATATCCG
GAGAGTTATATTGAGCANATCCCCCCGGTGAAGGATTTAACCGTGTTATC
TCGTTGGAATATTCATGGCGTATTTTGGATGATAACGAGGCGCAAAAAAT
GAAAAGTACTCTAGCAATTGTGAGCGGACAACAATTTCACACAGGAAACA
GCTATGACCATGATTACGCCAAGCTCCGAGATCTGGACGAGCTTTTTTTT
TTTTTCTCGGGAAGCGCGCCATTGTGTTGGTACCCGGGAATTCGGCACGA
GGGAGATCGAGGAGCTATGGAGGAGACAGAAGCCGGGGGGGCTATGGAGG
AGACCGTGGTGGTGGCAGTGGCTACGGTGGAGACCGAAGTGGAGNNTATG
GAGGAGACAGGAGTGGTGGCGGCTATGGAGGAGACCGAGGTGGGGGCTAC
GGAGGAGACCGAGGTGGCTATGGAGGCAAAATGGGAGGAAGAAACGACTA
CAGAAATGATCAGCGCAACCGACCATACTGATGACTGTTTTGAATGTTCC
TTTGTCTCTGACATGATCCATAGTGAAATTGCCAGAGTTTTGCCTGCTGC
TTTCCTCGTGGCCTCTTCTTGGGTGTGAAATTAAGTGACATTTGGATTTT
TATTTGGGTGGGAGGGCTGGGACAGTTTTTCT

SEQ ID NO: 12 (Thy2)
TTCCCTTTNGCCTNCCCGGGGGAAGGGCCCAAAAAAGGAANTTGCATTNG
CAATTGAAGTTCACCCNTTATTTTGCCCCACTTGGGAACGGTGATTTTTG
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NCCATGAAGGGGCTGGGAACCGACGAGGATTCTCTCATTGAGATCATCTG

CTCCAGAACCAACCAGGAGTGCAGGAAATTAACAGAGTCTACAAGGAAAT
GTACAGACTGATCTGGAGAAGGACATTATTTCGGACACATCTGGTGACTT
CCGCAAGCTGATGGTTGCCCTGGCAAAGGGTAGAAGAGCAGAGGATGGCT
CTGTCATTGATTATGAACTGATTGACCAAGATGCTCGGATCTCTATGACG
CTGGAGTGAAGAGGAAAGGAACTGATGTTCCCAAGTGGATCAGCATCATG
ACCGAGCGGAGCGTGCCCCACCTCCAGAAAGTATTTGATAGGTACAAGAG
TTACAGCCCTTATGACATGTTGGAAAGCATCAGGAAAGAGGTTAAAGGAG
ACCTGGAAAATGCTTTCCTGAACCTGGTTCAGTGCATTCAGAACAAGCCC
CTGTATTTTGCTGATCGGCTGTATGACTCCATGAAGGGCAAGGGGACGCG
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TGAAAATTAGGTCTGAATTCAAGAGAAAGTACGGCAAGTCCCTGTACTAT
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TGCTCACCATGCTTCCAGCTAACAGG

SEQ ID NO: 13 (Thy3)

AGGGNTTNTAAACGGGGCNAAGGTTTTAAAGCAATTTTGGGNAAATGGAG
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GTTGGGGAGGATTCAGATGCCCGCTTGGAGGCTGTTGNTACATGGTATTA
TTCTTTGNGCACTCCACGGATGATTATGCCTCCTTNTTCCCGGGCTNTGG
AGAATGCCACCCGGGATTACTTTATCATTTGCCCTATAATCGACATGNCC
AGTGCTTGGCAAAGAGGGCCCGAGGAAACGTCTTCATGTACCATGCTCNT
GAAAACTACGGCCATGGCAGCCTGGAGCTGCTGGCGGATGTTCAGTTTGC
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AGAAGAGCCTGTCGCTGAAAATCATGCAGTACTTTTCCCACTTCATCAGA
TCAGGAAATCCCAATTACCCTTATGAGTTCTCACGGAAAGTACCCACATT
TGCAACCCCCTGGCCTGACTTTGTACCCCGTGCTGGTGGAGAGAACTACA
AGGAGTTCAGTGAGCTGCTCCCCAATCGACAGGGCCTGAAGAAAGCCGAC
TGCTCCTTCTGGTCCAAGTACATCTCGTCTCTGAAGACATCTGCAGATGG
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ACTACAGCAAGTGACCAGCCCTTGAGCTCCCCAAAAACCTCACCCGAGGC

TGCCCACTATGGTCATCTTTTTCTCTAAAATAGCCACTTACCTTCAATAA
AGTATCTACATGCGGGAAAAAAAAAAAAAAAAA

SEQ ID NO: 14 (Thy5)

CGCCTGACTATCTTATATGATCTGCNGAAACTGNATGTATCCAAGTAAGT
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NCCNGCCACGGTGACANNAAACCGGGTNTNGGTCNGGGNANGTTGGNTCN
TTCNCTTNCGNCAGAATCCCTTNTTCATTCCTCTTCTCTGTGTTCATTCC
TCTTCTGTGCTGTTCTGAAGCTTCTACCAATACTCTTTCCATATTGTCTT
TTTCAGTGAAGAGAAATGCATTCAAGATTAGGTCCCTCCTGTCTATCCAG
TTTCAGGATTTTATGTTGTTTTATACACAGTTATTTCAGTATAGAAACTG
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AACTGTCCAACTTCAGTTTTTCATAAGATTAAACTTCTTACGATCAAATT
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SEQ ID NO: 15 (Thy6)

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GATCTTGCAGAACTTCGGCAACCATTTCCTCTTTGAAGAGNGGACANCCA
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TTTNCAGGNTGAATTGGAAANCCGTTCTAATCAGGTGCGATGTGCAGAGA
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GACAAGAATATGAAACAAAATTGAAAGGATTGATGCCAGCATCCCTAAGA
CAAGAACTTGAAGACACCATTTCCTCCCTAAAATCACAGGTTAATTTTCT
GCAAAAGAGAGCTTCCATCCTTCAGGAAGAACTGACTACATATCAAGGCA
GAAGGTAACTGCACGAGAGAATGCAACGGATGCAATTTCCAGGCTGTGCT
GTGGACTTCTTCCAGCAGGTTTGAAGATTTGGATATTGTAAACTGTGAGA
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CATCATTCATAAAAAAAAAAAAAAAA

SEQ ID NO: 16 (Thy9)

CGGGAATNTCGNTANGTCGAACTGAGGAGACAGAGACGCAAGAGAAAAAT
CCACTGCCTTCCAAAGAAACGATTGAACAGGAGAAGCAAGCAGGCGAATC
GTAATGAGGCGTGCGCCGCCAATATGCACTGTACATTCCACAAGCATTGC
CTTCTTATTTTACTTCTTTTAGCTGTTTAACTTTGTAAGATGCAAAGAGG
TTGGATCAAGTTTAAATGACTGTGCTGCCCCTTTCACATCAAAGAACTAC
TGACAACGAAGGCCGCGCCTGCCTTTCCCATCTGTCTATCTATCTGGCTG
GCAGGGAAGGAAAGAACTTGCATGTTGGTGAAGGAAGAAGTGGGGTGGAA
GAAGTGGGGTGGGACGACAGTGAAA

SEQ ID NO: 17 (Thy11)

TCGGAACAGCNAACAAAGACCATGTCAAGGTCCCAAAGCCCACGGGGGTG
AAGAAGGGATGGCAGNGNGNATATGCAGTCGTCTGTGACTGCAAGCTCTT
CNTGTATGATCTGCNTGAAGGAAAATCCACCCAGCCTGGTGTCATTGCGA
GCCAAGTCTTGGATCTCAGAGATGACGAGTTTTCCGTGAGNTCAGTCCTG
GCCTCAGATGCATTCATGNTACACGCCGAGATATTCCATGTATATTCAGG
GTGACGGCCTCTCTCTTAGGTGCACCTTNTAAGACCAGCTCTNTGCTCAT
TNTGACNGAAAATGAGAATGAAAAGAGGAAGTGGG

SEQ ID NO: 18 (Thy12)

GCTCCGGAAATTTTGGACGGGNCTTTTTTTTTTTTTTCTCGGGGAAGCG
GCNCCCATTTGTGTTTGTTACCCCGGGAATTTCGGCNACGGGGACCAAAA
TTGAAGTTGGACAAACGGTTCTTTGCACAAATTGACGTACCATTTTCACA
GTTTAATTCGTGAAGGTTTGGAAAGGTTAACCANGTTCTTATTAGTACTT
TTCATAAGCAGTTGGATTTTCTGAAAAATACAGTAACATAATTTTTAGTA
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AAAACCTGTTTATTACATGAATGCTACTTATGAGAATTTAAAATATGGGT
TCACTTCCTATTTTCCACAAGTCTTTGACTTGTTTATTTACTAAATTAAC
AGAACGTGGGATGCAGTTTTTTAAGTTAGCAACTTCCTTAGGGTTACTGG
GAAGTAGAGTAATTATGAAAAAGGGAACACTTCAATTATTGTATAAAAGA
TTGCTTTGCATACTGATTACTTCTTGAACCCCAAAAAGTGCTATTTAGAG
GCAAGGGCCCATTTTGTGCCCATTAAAAGAAATATACAGGTGAATGTCTG
TCTCATCCCTCTAATCATATGTAATAAAATTATATCGCTGTCAATAACAG
CAAAGATAATGATATATTAATTTTAACAGCAGTTAGAACCAGAAGGAAAA
GGCTGTTATACAGAAAAACATACAAATATGTAGGTAGAAGTGAAAAACTG
AAGAATGTGGAGTGTTTACTGTCCCGTTACTCACACAGACGTGCTGGATT
CAACACCCACGCTGAATCTCCATTTATTCCACGGAGGTGGAGTTCACCAT
GGTTCGACTGCCCACCAGATCCCCAAATGTCAAAGTGAAACAAAACTCAG
TGAAT

SEQ ID NO: 19 (Thy14)

CACTTGAAATTTTNGTTAGGNCCCTTTGGGNTTCCCTTNTTTCTTGTNNT
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TCAATGGAACTGTTAGTTTTNCTCTGGGGATTCTTTAACTTTAGAGCCAT
TTNCTTTTTCTTCAAAANTGATGAACTTTTTGGTTTGAAAGGCTTANGGA
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GCTAACAGTTCAACTACCGAGATTATTTGATAACCTGGGTTTTCTCATTC
ATCCATCAAGCACCATCAACCAGTCAGCCATTATTATTTATATATGTATT
ACCAAAAGCAGTCTATCTGCCTGTGACCTCCAATGTACACTGCCAAACAC
AAGAGTAGGACACATCTGTTCTGGGTTCTTGACCTATCTGTCTCCAATTC
ATCTCCCCTTTTCAGCCATTTCAACAAACTACTCTTTGGAGCTCTGAGAT
GACATCTTGTTGTTTTATATAGATGTATCTTTTAAAAATAGTTCACGTTT

GGAGAATTCTTTTGTACTCATTTGCTTTTTGTCTGAGAACCATGTCTATT
TTTATAACTGGAGTGTGAGTTCTGTATCTTCTCACATTCTGTATACTGTA
TCCATTT

SEQ ID NO: 20 (Thy15)

GGCGGCTTTGTNGCAGNNAAAGGCNGGNTNNCNAGGGATNGTTNGGACAN
AAAGGTTTTGAAGGATTGCGGAAGGAAGCAGNTTGATTNGGNGGNTANTG
ACCCAAGCCAATCCAAGGTTTTNANCACGGNTGAAATTTGGAAACCNGTT
NCTAAATNCAGGTGCGGATGTGCAGGAGAAAAAATTACCAACCNCAAGGA
NTTTGGAGTCACAGGAACNGGTTAACTTACATANGACAAGACTNTTGAAA
CCAAAATTGAAAGGATTGATGCCAGCATCCCTAAGACAAGAACTTGAGAC
ACCATTTCCTCCCCTAAAGTCACAGNTTAATTTTCTGCAAAAGAGAGCTT
CCATCNTTCAGGAAGAACTTGANTACATATCAAGGCAGAAGGTAACTGCA
CGAGAGANTGCAACGGATGCAATTTCCAGGCTGTGCTGTGGACTTCTTCC
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TTAAATCCTTAAATGTANTTAAGATCATAAAAACATGCATCATTCATACA
CTAGTGGGGTGGATTATTTGTGTCNTGCCTAAGTTATTTTTTTAACATTC
CTTTATTTCCGATTTTCATGTTTGTGTGCATTTGAGTATGTGCTGAGAAC
TGCTTATATTGGGCAAAGTGATTTCCTATGATATGCCTTGTTAATCCTTT
TGCATAGAATTTTACCAGTTGCGTACGATCAAAATCACGTTTGTAGTATC
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GTTATTAAAATATTATTTTGTAAAAAAAAAAAAAAA

SEQ ID NO: 21

gi|2723456|dbj|D30612|D30612 Homo sapiens mRNA for repressor protein
, partial cds

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SEQ ID NO: 22

>gi|1503985|dbj|D86956|D86956 Human mRNA for KIAA0201 gene, complete cds

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SEQ ID NO: 23

>gi|415818|emb|X65550|HSMKI67 H.sapiens mki67a mRNA (long type) for antigen of monoclonal antibody Ki-67

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SEQ ID NO: 24

>gi|415820|emb|X65551|HSMKI67A H.sapiens mki67a mRNA (short type) for antigen of monoclonal antibody Ki-67

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SEQ ID NO: 25

>gi|29860|emb|X55039|HSCENPB Human hCENP-B gene for centromere autoantigen B (CENP-B)

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AAGAGGAGGAAGATGAGGAGAGCTCCTCGGAGGGCTTGGAGGCTGAGGACTGGGCCCAGGGAGTAGTGGA
GGCCGGTGGCAGCTTCGGGGCTTATGGTGCCCAGGAGGAAGCCCAGTGCCCTACTCTGCATTTCCTGGAA
GGTGGGGAGGACTCTGATTCAGACAGTGAGGAAGAGGACGATGAGGAAGAGGATGATGAAGATGAAGACG
ACGATGATGATGAGGAGGATGGTGATGAGGTGCCTGTACCCAGCTTTGGGGAGGCCATGGCTTACTTTGC

CATGGTCAAGAGGTACCTGACCTCCTTCCCCATTGATGACCGCGTGCAGAGCCACATCCTCCACTTGGAACACGATCTGGTTCATGTGACCAGGAAGAACCACGCCAGGCAGGCGGGAGTTCGAGGTCTTGGACATCAAAGCTGAGTCACTGGACCTAGCTGTGCCCCCAACCTAGATTGGCAGCACCACCCCAGGGCAGAGGACTCTCTGGGCACCCGCTGTGCATGGAGCCAGAGTGCAGAGCCCCAGATCCTTTAGTAATGCTTCCCCTGGTCCTGCAACAGGCCCGGTCACCTCGGCCGGGCCCGGGGCTGAGGTCAGCCTCACTGCCTGCTTATTGCCTCTTTCTCAGAATCCTCTTTCCTCCCCATTTGGCCCTGGGCTCAGGGGACCAGGTGGGGCGGGTGGGGAGCTGTCCGGTGCTACCACACCGTGCCCTCAGTGGACTAACCACAGCAGCAGCCAGGGATGGGCCCTGGAGGTTCCCGGCCGGAGAGTGCCTCTCCCCTCTGCCATCCACGTCAGGTCTTTGGTGGGGGACCCCAAAGCCATTCTGGGAAGGGCTCCAGAAGAAGGTCCAGCCTAGGCCCCCTGCAAGGCTGGCAGCCCCCACCCCCACCCCCCAGGCCGCCTTGAGAAGCACAGTTTAACTCACTGCGGGCTCCTGAGCCTGCTTCTGCCTGCTTTCCACCTCCCCAGTCCCTTTCTCTGGCCCTGTCCATGTGACTTTGGCCCTTGGTTTTCTTTCCAGATTGGAGGTTTCCAAGAGGCCCCCCACCGTGGAAGTAACCAAGGGCGCTTCCTTGTGGGCAGCTGCAGGCCCCATGCCTCTCCTCCCTCTCTCTGGCAGGGCCCATCCTGGGCAGAGGGGCCTGGGGCTGGGCCCAGAGTCCAGCCGTCCAGCTGCTCCTTTCCCAGTTTGATTTCAATAAATCTGTCCACTCCCCTTTTGTGGGGGTGAACGTTTTAACAGCCAAGGGTGCATCCTTCATGGTCTGGGCTTGCGTCTGTCTTGGGGGACTTATTCGTCCTGGCTCTCTTTGGTCCTTGCTCTGGTGGGACATGGAGGCAAGTGTTGAGAGGGTTGCCCTGACCGGAAGAGGGGCAGGAGGAGACCTCAAGCTT

SEQ ID NO: 26

>gi|1628402|emb|X98893|HSTAFII68 H.sapiens mRNA for TBP associated factor, TAFII68

GTTGTTCTCGGCGGGCTGTGGGGCCTCCGCGCCGCGGCCGTTAGTCATGTCGGATTCTGGAAGTTACGGT
CAGTCTGGGGGTGAGCAGCAAAGTTATTCTACCTATGGAAATCCAGGCAGCCAAGGCTATGGACAAGCAT
CACAAAGCTATTCTGGCTATGGGCAAACGACTGATTCCTCTTATGGACAGAACTACAGCGGTTACTCCAG
TTATGGACAAAGTTATTCACAGTCCTATGGTGGTTATGAGAATCAAAAGCAGAGCTCATATAGCCAGCAA
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ATATGATGAGCAGTCAAATTATGATCAGCAGCATGATTCCTATAGTCAAAACCAGCAGTCCTATCATTCA
CAAAGGGAAAACTACAGCCACCACACACAAGATGACCGTCGTGATGTGAGTAGGTATGGAGAAGATAATA
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GACAGGATCAAGTGGTGGTGACCGCGGTGGCTTCAAAAATTTTGGTGGTCACAGGGATTATGGACCCAGA
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TGTTTTGAATGTTCCTTTGTCTCTGACATGATCCATAGTGAAATTGCCAGAGTTTTGCCTGGTGCTCTCC
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GTTTTTCTTCTAGAAATGTCTGTTGAGATTTCCCCCTTTAGTTTCCAACCTTCTCCCCAACCCTTGGAGC
TAAATGCGTTGTAAAATATTGCCAAAATGAAAAGTGTTTTGTAATACTGCAATAAAGGCTGCTTGTTTTT
GTGGAAAAAAAAAAAAAAAAAAAAA

SEQ ID NO: 27

>gi|219909|dbj|D00017|HUMLIC Homo sapiens mRNA for lipocortin II, complete cds

CATTTGGGGACGCTCTCAGCTCTCGGCGCACGGCCCAGCTTCCTTCAAAATGTCTACTGTTCACGAAATC
CTGTGCAAGCTCAGCTTGGAGGGTGATCACTCTACACCCCCAAGTGCATATGGGTCTGTCAAAGCCTATA
CTAACTTTGATGCTGAGCGGGATGCTTTGAACATTGAAACAGCCATCAAGACCAAAGGTGTGGATGAGGT
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CGAGGACTCTCTCATTGAGATCATCTGCTCCAGAACCAACCAGGAGCTGCAGGAAATTAACAGAGTCTAC
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ACCGAGCGGAGCGTGCCCCACCTCCAGAAAGTATTTGATAGGTACAAGAGTTACAGCCCTTATGACATGT
TGGAAAGCATCAGGAAAGAGGTTAAAGGAGACCTGGAAAATGCTTTCCTGAACCTGGTTCAGTGCATTCA
GAACAAGCCCCTGTATTTTGCTGATCGGCTGTATGACTCCATGAAGGGCAAGGGGACGCGAGATAAGGTC
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ACGGCAAGTCCCTGTACTATTATATCCAGCAAGACACTAAGGGCGACTACCAGAAAGCGCTGCTGTACCT
GTGTGGTGGAGATGACTGAAGCCCGACACGGCCTGAGCGTCCAGAAATGGTGCTCACCATGCTTCCAGCT
AACAGGTCTAGAAAACCAGCTTGCGAATAACAGTCCCCGTGGCCATCCCTGTGAGGGTGACGTTAGCATT
ACCCCCAACCTCATTTTAGTTGCCTAAGCATTGCCTGGCCTTCCTGTCTAGTCTCTCCTGTAAGCCAAAG
AAATGAACATTCCAAGGAGTTGGAAGTGAAGTCTATGATGTGAAACACTTTGCCTCCTGTGTACTGTGTC
ATAAACAGATGAATAAACTGAATTTGTACTTT

SEQ ID NO: 28

>gi|37173|emb|X05615|HSTHYRR Human mRNA for thyroglobulin

GCAGTGGTTTCTCCTCCTTCCTCCCAGGAAGGGCCAGGAAAATGGCCCTGGTCCTGGAGATCTTCACCCT
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TGTGAGCTGCAGAGGGAAACGGCCTTTCTGAAGCAAGCAGACTACGTGCCCCAGTGTGCAGAGGATGGCA
GCTTCCAGACTGTCCAGTGCCAGAACGACGGCCGCTCCTGCTGGTGTGTGGGTGCCAACGGCAGTGAAGT
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TTACTGAGTGGCTACATTAACAGCACAGACACCTCCTACCTCCCTCAGTGTCAGGATTCAGGGGACTACG
CGCCTGTTCAGTGTGATGTGCAGCATGTCCAGTGCTGGTGTGTGGACGCAGAGGGGATGGAGGTGTATGG
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GGGGTGGGAGATAAGTCACCACCCCAGTGTTCTGCGGAGGGAGAGTTTATGCCTGTCCAGTGCAAATTTG
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CTTCAGTTCCTTCCAGAGGAGGTTCCCTGAGGTATCTGGGTATTGCCACTGTGCTGACAGCCAAGGGCGG
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CATCTCTGGCAGATTCCGATGCCCCACAAAATGTGAAGTGGAGCGGTTTACAGCAACCAGCTTTGGTCAC
CCCTATGTTCCAAGCTGCCGCCGAAATGGCGACTATCAGGCGGTGCAGTGCCAGACGGAAGGGCCCTGCT
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CCTGCCCACCCACGATCAAGGAGCTCTTTGTGGACTCTGGGCTTCTCCGCCCAATGGTGGAGGGACAGAG
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SEQ ID NO: 29

>gi|339688|gb|M17733|HUMTHYB4 Human thymosin beta-4 mRNA, complete cds
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AATGAGGCGTGCGCCGCCAATATGCACTGTACATTCCACAAGCATTGCCTTCTTATTTTACTTCTTTTAG
CTGTTTAACTTTGTAAGATGCAAAGAGGTTGGATCAAGTTTAAATGACTGTGCTGCCCCTTTCACATCAA
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GAACTTGCATGTTGGTGAAGGAAGAAGTGGGGTGGAAGAAGTGGGGTGGGACGACAGTGAAATCTAGAGT
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SEQ ID NO: 30

>gi|1743866|gb|U70063|HSU70063 Human acid ceramidase mRNA, complete cds
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SEQ ID NO:31 -- Oligo N1, Ki67 sense, Nhe, 6His, 5610:
ATTGCTAGCCACCACCACCACCACCACAAACTGGACCCAGCAGCAAGTGTAAC

SEQ ID NO: 32 -- Oligo N2, Ki67 antisense, EcoRI, 6420:
CGGGAATTCCTATAGAGCCTCAGCCTTTTCCTTAGG